IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

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IN RE BRIMONIDINE PATENT LITIGATION) **C.A. 07-md-1866-GMS**

- - -

Wilmington, Delaware
Tuesday, March 10, 2009
8:55 a.m.
Day 2 of Trial

- - -

BEFORE: HONORABLE GREGORY M. SLEET, Chief Judge

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THE COURT: Good morning.

(Counsel respond "Good morning.")

MS. BROOKS: Your Honor, with the Court's permission, Mr. Marsden isn't here yet, but may we proceed without him?

THE COURT: Absolutely, if he doesn't mind.

MR. BREISBLATT: Thank you, Your Honor.

... OREST OLEJNIK, having been previously sworn as a witness, was examined and testified further as follows ...

MR. BREISBLATT: Your Honor, may I ask permission now to approach the witness at some time during the examination?

THE COURT: You have leave to approach freely.

MR. BREISBLATT: Thank you.

CROSS-EXAMINATION CONTINUED

BY MR. BREISBLATT:

Q. **Dr. Olejnik, I would like to visit a little bit with you on the timeline.**

Now, you mentioned that Allergan had tried or thought about a number of other solutions before it went to the Refresh Tears product. Is that correct?

A. **That's correct, before we started using excipients that are contained in the Refresh product.**

Q. **Well, I will tell you what, we will get to that in a**

second. Am I correct that all of those thoughts, those documents that were put up on the screen, those are all Allergan confidential internal documents? Am I correct?

A. For the most part, yes.

Q. So they weren't publicly known. Correct?

A. For the most part, yes.

Q. So let's focus on what is publicly known. Refresh Tears goes to market in approximately June of 1997. Am I correct?

A. I would have to verify that. But if you say so.

Q. Do you have any question, sir? Let's verify it. I don't want any questions. Let me show you what we previously marked as DTX-10. Instead of giving you the whole volume, I will just pull out the pages I want.

MR. BREISBLATT: May I approach the witness, Your Honor?

THE COURT: You have that leave, counsel.

BY MR. BREISBLATT:

Q. Do you recognize the cover as an Allergan document, sir?

A. It's an Allergan document.

Q. If you turn to Page AGN 59380, the Bates number, do you have that?

A. 59380, yes, I do.

Q. See where it says "Refresh Tears," about middle of the

page?
A. Yes.
Q. It says "Refresh Tears, which also contains Purite," and then it goes on to say, "It's been marketed in the U.S. and Canada since June of 1997"?
A. Okay.
Q. Are we in agreement now, Refresh Tears on the market, publicly available June of 1997?
A. Yeah, agreed.
Q. It was shortly after it went to market that Allergan decided to use Refresh Tears along with brimonidine tartrate in a formulation. Am I correct?
A. It started using excipients as part of the formulation.
Q. You said that a couple times. Let me show you what has been marked as PTX-295.
Allergan document, sir. Am I correct?
A. It says Allergan, Inc., down in --
Q. It is dated September 27, 1998. Am I correct, sir?
A. That is correct.
Q. And this is about when you were beginning the Phase 3 investigatory meeting. Is that correct?
A. Well, I need to go through the --
Q. Looking at the cover, sir, do you have any question? Does it say Phase 3 Investigative Meeting?

A. **Phase 3 Investigative Meeting in Atlanta, Georgia.**

Q. **Thank you. Brimonidine Purite. Am I correct?**

A. **That's brimonidine Purite, yes, sir, that's correct.**

Q. **All right. Now, let's go to the first page after that, 92537. It talks about Purite has a trademark, because Purite belonged to a different company. Is that correct?**

A. **Yes.**

Q. **Do you see where it says, "Allergan has worldwide exclusive rights for ophthalmic applications for Purite," at the bottom of it?**

A. **Yes, I see that.**

Q. **And you have no reason to doubt that, do you, sir?**

A. **Well, it says what it says. I need to go look at the --**

Q. **It's an Allergan document, sir?**

THE COURT: Let him finish the answer, counsel. Mr. Maurer can't record both of you.

THE WITNESS: I would have to look at the licensing agreement. If it says what it says, I would assume that is correct.

BY MR. BREISBLATT:

Q. **Are you disputing this Allergan document, sir?**

A. **No, I am not disputing it.**

Q. **And it says, under Ophthalmic Hydrogel Lens, Saline Solution and Refresh Tears.**

Am I correct?

A. **You are correct.**

Q. **Let's go to the next page. The cover of this document said Brimonidine Purite on it, didn't it?**

A. **On the front page, yes.**

Q. **Now we get to the third page of the document, 92358, and is that Refresh Tears, sir?**

A. **It says Refresh Tears, yes.**

Q. **And that's a picture of the Refresh Tears bottle right out of Allergan, isn't it, sir? Right off the shelf?**

A. **Yes.**

Q. **"A multi-dose preserved tear formulated with carboxymethylcellulose and Purite, a technologically advanced preservative which dissipates with light."**

Right?

Do you see that, sir?

A. **Correct.**

Q. **That was publicly known, wasn't it, sir?**

A. **I am assuming it was in the package insert. I don't know, if this was in an investigators' meeting it would have been under confidentiality. So I can't assume it would have been publicly known.**

Q. **Which part, sir? That it dissipated in light?**

A. **That it dissipates in light.**

Q. **But Purite wasn't even your product, was it?**

A. **It's an Allergan product.**

Q. **Purite, sir?**

A. **You mean -- I was thinking of Refresh Tears.**

Q. **Refresh Tears is?**

A. **It was licensed from Bio-Cide.**

Q. **There you go.**

Let's look at the Refresh Tears formulation. The next page.

Let me ask you this, sir: Was it your idea to use Refresh Tears in brimonidine tartrate?

A. **If I used Refresh Tears in brimonidine tartrate, the brimonidine tartrate would have precipitated out. This is a pH of 7.7. It was my idea, together with Edward, to look at the excipients that are contained with Refresh Tears --**

Q. **Let's take a step back, sir. One more time.**

MS. BROOKS: Your Honor, I apologize. Could the witness be allowed to finish his answer?

THE COURT: Please, Mr. Breisblatt.

MR. BREISBLATT: I thought he was, sir. I am sorry.

BY MR. BREISBLATT:

Q. **Are you done, sir?**

A. **Yes, thank you.**

Q. **One more time, sir. Was it your idea and your idea alone to use Refresh Tears?**

A. **I had -- it was my idea to use, together with Edward, the use of these excipients that are present in Refresh Tears.**

Q. **Now, you knew the excipients were present in Refresh Tears because you got a hold of Refresh Tears. Right?**

A. **There is a composition of Refresh Tears, yes.**

Q. **Now, here is the list of Refresh Tears. These are the ingredients in Refresh Tears. Am I correct, sir?**

A. **You are correct.**

Q. **Which one of these ingredients did you not use in the brimonidine formulation?**

A. **Well, aside from the pH -- I have to go back and revisit on viscosity -- I used, we used all the ingredients that are listed there, Purite, CMC, sodium chloride, potassium chloride, calcium chloride, magnesium chloride, boric acid, not necessarily in those concentrations.**

Q. **As I understand it, sir, you used all of the ingredients of Refresh Tears. Am I right?**

A. **We used the ingredients that are present in Refresh Tears, correct.**

Q. **Thank you. In fact, if we turn the page, we have a brimonidine Purite formula comparison. And these are Allergan words, not mine. Do you see the words "Same as Refresh Tears" and the checkmark?**

A. **Yes.**

Q. **Now, let's look at the electrolyte comparisons. Let's go a page, next page.**

Whoever prepared this document was nice enough to compare a bunch of artificial tears products along with Refresh Tears. Am I correct?

A. **There is a table here that does a comparison, yes.**

Q. **One of the things they noted down at the bottom is it says, "In brimonidine Purite formula, EDTA, EDTA sodium is not required to meet U.S. PET criteria." Correct?**

A. **That's what it states.**

Q. **And I understand by removing that, it permitted two more ingredients that were in Refresh Tears to be used. Am I right?**

A. **That is correct.**

Q. **Now, one of the features of Refresh Tears, let's go to the next page, and it's something that is present in the combination of brimonidine tartrate and Refresh Tears, is the carboxymethylcellulose, CMC. Am I correct?**

A. **Correct.**

Q. **And now the person who wrote this said that CMC is a superior mucoadhesive, which provides longer retention time. Do you see that?**

A. **Yes.**

Q. **And you agree with that statement, don't you, sir?**

A. **No, I don't.**

Q. **So at least in Allergan there is a dispute, somebody in Allergan believes that carboxymethylcellulose is a superior mucoadhesive, which provides longer retention time. Am I correct? Somebody at least at Allergan believes it. Right?**

A. **That's a statement. It has to be qualified based on what that statement refers to.**

Q. **The statement is what it is. Am I right, sir?**

A. **Well, that's what it says in the print here.**

Q. **Thank you.**

Now, it says The Features of Purite. Stabilized oxychloro complex, proprietary to Allergan.

That is the Purite. Right?

A. **Excuse me. Are you reading off another page?**

Q. **Yes. We have moved onto the next page, sir, 292363. And when it says it's proprietary to Allergan, that's that worldwide license we saw earlier. Correct, sir?**

A. **Yes.**

Q. **Now, Refresh Tears is an artificial tears product. Am I correct?**

A. **You are correct, yes.**

Q. **That was developed in Allergan in a group different from your group. Am I right?**

A. **I believe that to be the case, yes.**

Q. **In other words, you didn't develop Refresh Tears, did**

you, sir?

A. **I was involved on the periphery of that, because it needed to be a project that got budgeted. So I do believe that I was involved in that process.**

Q. **In the budgeting process?**

A. **To support that project.**

Q. **And the reason why, by 1997, you were -- you weren't a bench scientist any longer, were you? You were now in management. Am I correct?**

A. **That is true.**

Q. **In the management function, you had this budget function as well. Correct?**

A. **I had a budget function. That doesn't mean the bench scientists themselves weren't involved in budgeting. We had to do costs, timing, and resources.**

Q. **So the answer to that is yes, sir?**

A. **It involved a number of people. But I was involved in budgeting aspects, yes.**

Q. **So the answer to my question was yes?**

Sir, if you can't answer one of my questions yes or no, please let me know. We will let you explain, but let me know if you can't answer my question. This examination will go a lot quicker.

A. **Okay.**

Q. **Thank you.**

Now, one of the purposes of Refresh Tears was to treat something called dry eye. Isn't that right?

A. **The symptomatic relief of dry eye.**

Q. **Remember what I said, sir. Could you answer my question yes or no? Was one of the purposes of Refresh Tear to create a condition called dry eye? Yes or no?**

A. **No.**

Q. **Thank you. Now, it's an artificial tears product. Yes or no?**

A. **Yes.**

Q. **And one of the purposes of an artificial tear product is to stay in the eye. Yes or no?**

A. **Yes.**

Q. **And one of the ingredients in Refresh Tears was CMC. Yes or no?**

A. **Yes.**

Q. **And it was one of the things that helped it stay on the eye, didn't it?**

A. **I don't know.**

Q. **Thank you.**

Now, Purite is a preservative, isn't it?

A. **Yes.**

Q. **And CMC is a viscosity agent, isn't it?**

A. **It's a viscosity agent, yes.**

Q. **Preservatives don't help anything stay on the eye, do**

they?

A. They can, depending upon the preservative.

Q. Was that a yes or a no, sir?

A. A maybe.

Q. Now, you said yesterday that it was not as easy as taking Refresh Tears and adding brimonidine tartrate to it. Correct?

A. I believe I said that, yes.

Q. Let me show you JTX-043.

Again, sir, you recognize JTX-043 as an Allergan document. Am I correct?

A. Yes.

Q. Would you turn to Page 0544021, and do you see this is an executive summary from A. Aswat? Is that correct?

A. Yes.

Q. And under the heading of Executive Summary, it says, "The overall objective for this meeting was to review the potential formulations for brimonidine-X (U.S. development only at this time) that will meet the marketing timeline and requirements."

Do you see that?

A. Yes.

Q. Why don't you look at the bottom of that. Do you see where there is an agreement that the three-year exclusivity with the new formulation is not enough time to maintain the

product line extension?

Do you see that?

A. **Yes, I do.**

Q. **"And the patent protection is required, a marketing requirement, based upon actual on-market time that would be left after launch of a product with only three-year exclusivity."**

Do you see that?

A. **Yes, I do.**

Q. **Right before that it has, "The brimonidine-X subteam meeting of June 18, 1997."**

Do you see that date?

A. **Yes, I do.**

Q. **It says, "Proposal. Evaluate two formulations of Refresh Purite. Patent expires 2012."**

That patent they are talking about, sir, are you aware that is the '078 patent that is at issue in this lawsuit?

A. **No. I wasn't aware of that at that time.**

Q. **But you were aware there was a patent that they were concerned about?**

A. **I was aware that there was a patent, yes.**

Q. **And it says Refresh Purite and it says CMC, sodium chloride. Do you see that?**

A. **Yes, I do.**

Q. **So the two major ingredients that they were looking at from Refresh Tears at that time was the CMC and the sodium chloride. Am I correct?**

A. **That's what it says, yes.**

Q. **This was before you ever combined the two. Am I right?**

If you don't know, just say you don't know. I will help you with that.

A. **I believe, yes.**

Q. **Beneath it says, "Proceeding with evaluating the Refresh Purite evaluation. Data will be available in approximately two weeks."**

Am I correct?

A. **Yes.**

Q. **Just to put it in context, do you see right below that it says, "The meetings from June 10, 1997. And it says, The team leader for the brimonidine project starting July 19th, '97 will be you. Correct?**

A. **Yes.**

Q. **So you are not even the team leader of the brimonidine project until July of 1997. Am I right?**

A. **That's correct.**

Q. **And the decision has already now been made to go forward with and at least try the Refresh Tears/Purite combination. Am I correct?**

A. **Could you repeat that again, please?**

Q. **Sure. You don't become the team leader until July 1997. Am I correct?**

A. **Yes.**

Q. **Before you become the team leader, a decision has already been made to go forward and try the Refresh/Purite combination. Am I correct?**

A. **In June, yes.**

Q. **Thank you. Let me show you what has been marked as JTX-080. It's a large document, but we pulled out some pages from it.**

You are familiar with Angel Padilla. Am I correct?

A. **Yes.**

Q. **And he was more of a bench scientist. Am I correct?**

A. **I don't know what his -- I don't remember his title. But he was a lab scientist, yes.**

Q. **Now, one of the things you do at Allergan is you have lab books. Am I correct?**

A. **Yes, we do.**

Q. **And if we look at JTX-80, if you look at the page that's marked AGN 066779, this is Mr. Padilla's lab book. Am I correct?**

A. **I am just looking, AGN 066780.**

Q. **66779.**

A. **Excuse me.**

That's correct.

Q. **If we turn to Page -- there is a bunch of blank pages, if you turn to page AGN 0066787, do you have it?**

A. **Yes, I do.**

Q. **The date of this is June 25th, 1997?**

A. **Correct.**

Q. **And that's right after the decision is made to try the brimonidine/Refresh Tears combination. Am I correct?**

A. **Correct.**

Q. **Now, if we go down to the -- you see where it looks like, some of it is cut off, but it's like o-s-e and there is a colon. And the first sentence under it says, "To formulate"?**

A. **Did you say o-s-e? Did I hear you correctly?**

Q. **Yes. It probably says "purpose," but the p-u-r has been cut off.**

That first sentence, sir, doesn't it state, "To formulate a new brimonidine formula using the Refresh Tears base"?

A. **That's what it says, yes.**

Q. **And this is the guy who is actually combining the ingredients. Am I right?**

A. **He is the one who was directed to do that work, yes.**

Q. **And so what he did is took Refresh Tears and he put**

brimonidine tartrate in it, didn't he?

A. **Well, I don't know exactly what he did. I wasn't there over -- looking over his shoulder.**

Q. **It says Refresh Tears base, sir. It doesn't say excipients. It says Refresh Tears, doesn't it?**

A. **It says Refresh Tears base.**

Q. **If we look down below, for the formulas, you find all the ingredients that are in Refresh Tears, don't you?**

A. **Yes.**

Q. **So he took a bottle of Refresh Tears off the shelf, and he put brimonidine tartrate in it, didn't he?**

A. **That is not the way we do our studies, by taking bottles off the shelf, no.**

Q. **You are right, because you are Allergan where you make Refresh Tears, so we got it from the lab?**

A. **In the lab we do not have products sitting on the shelf.**

Q. **You are right. So we went to the supply room and they gave him some Refresh Tears?**

A. **Highly unlikely.**

Q. **But he says he used the Refresh Tears base, and it's all the ingredients of Refresh Tears, in their exact percentages. Right?**

A. **By what you said there, that is correct. When you do composition work, you use the raw materials that have been**

released, qualified in the lab to be used.

Q. Same exact percentages as in the bottle off the shelf, if you were one skilled in the art buying it.

A. Just bear with me for a moment.

(Pause.)

A. It's the same excipients. Just different pH.

Q. Now, the pH you said of Refresh Tears is what, 7.7?

A. 7.7.

Q. So he was using a pH that looks like it's 7.5 and 6.8. Am I right?

A. Correct.

Q. That is one of the things a laboratory scientist does, is there are tools to adjust pH, aren't there, sir?

A. There are sodium hydroxide, hydrochloric acid, to adjust pH, yes.

Q. There are a lot of tools to adjust pH, aren't there, sir?

A. There are liquids that you can use.

Q. Now, if we turn the page to 66788, he says, "No precipitation at higher pH range 7.5 compared to previous info on brimonidine."

Right?

A. That's what it says, yes.

Q. So he did it, and what does he discover, without doing anything more? That this big fear of precipitation didn't

take place? No shards in the eye, no glass. Right?

THE COURT: Which question do you want him to answer?

MR. BREISBLATT: I am sorry, Your Honor.

BY MR. BREISBLATT:

Q. Am I correct, sir, that he says no precipitation at the higher pH range of 7.5?

A. That's what he observed there, yes.

Q. Thank you.

Did you see him write the word surprising result anywhere?

A. No.

Q. And after he did this test in June-July, you went forward with this formulation in August of the same year. Am I correct, sir?

A. Of 19 --

Q. 1997.

A. Is it August, or it might have been -- '97, might have to look at the timelines.

Q. Within a month, sir?

A. I would assume so.

Q. Thank you.

Now, let me put up Demo 2.

Can you see it on the screen in front of you, sir?

A. **Yes, I can.**

Q. **Now, is there anything that is listed under Brimonidine Tartrate -- do you see where it has a column that says Brimonidine Tartrate?**

A. **Are you talking about the red column?**

Q. **Yes.**

A. **Yes.**

Q. **Do you see all the words under the red column?**

A. **Yes.**

Q. **All the various descriptions?**

A. **Yes, I do.**

Q. **Am I correct, sir, that each one of those descriptions would include brimonidine tartrate?**

A. **Yes, they would.**

Q. **Now, let's look at the next column, the blue column. Do you see that?**

A. **Yes, I do.**

Q. **Do you see where it says, and I will take one more shot at it, Carboxymethylcellulose, CMC?**

A. **Yes.**

Q. **Do you see all the words under CMC under the blue?**

A. **Yes, I do.**

Q. **Would all those terms describe carboxymethylcellulose?**

A. **Prior to the work, no. But the work we had done, yes.**

Q. **So they all describe carboxymethylcellulose. Correct?**

A. **After the investigations we conducted, yes.**

Q. **Let's see. Polyanionic component. Wasn't it a polyanionic component before you did your work?**

A. **Yes.**

Q. **Wasn't it an anionic polymer before you did your work?**

A. **Yes.**

Q. **Wasn't it an anionic cellulose derivative before you did your work?**

A. **An anionic cellulose derivative, yes.**

Q. **And it was an anionic polymer. Correct?**

A. **It was a polyanionic polymer, yes.**

Q. **Your dispute with me is you are saying before you did your work in 1997, it was not a solubility enhancing component. Am I correct?**

A. **It was not known as a solubility enhancing component, an SEC, yes.**

Q. **You know there was literature out there prior to you doing your work that said exactly that, that it was a solubility enhancing component. Am I correct?**

A. **I would like to see that.**

Q. **Thank you.**

Let me show you what we have marked as Defendants' Trial Exhibit 341.

A. **Thank you.**

Q. **Now, you are familiar with the International Journal**

of Pharmaceutics. Am I correct?

A. Yes, I am. I referee papers for that journal.

Q. Were you refereeing papers in September of 1994?

A. I don't remember.

Q. How long have you been a member of the organization?

A. It's not a matter of organization. You get invited to be a referee by the editor.

Q. That is quite an achievement, isn't it?

A. It's an honor to be able to be asked, yes.

Q. This is an important journal, isn't it?

A. It's one of many good journals.

Q. Well read in the field?

A. I believe so.

Q. Now, the date on this copy is 19 September 1994. Am I correct, sir?

A. 1994, yes.

Q. Prior to you doing your work. Am I right?

A. Yes.

Q. Now, will you turn to AGN 0219705?

Actually, turn to AGN 0219707, we will look at the second column, we will go about halfway down, where it starts with, "In our study," do you see that?

A. Not yet, sir.

THE COURT: Which column are you?

MR. BREISBLATT: The right-hand column.

THE WITNESS: This is on 0707?

BY MR. BREISBLATT:

Q. **Yes. And I am starting with where it says, "In our study, the addition of a very small amount," it says .25 percent weight per volume, "of PVP, CMC," then it says, "or HPMC resulted in a significant increase in the aqueous solubility of most of the drugs tested. The solubility enhancement of both CMC" -- that's what we have been talking about, right, sir?**

A. **We are talking about CMC, yes.**

Q. **And "--and PVP was on the average about 1.7-fold." Then it goes on further and says, "The polymers mainly interact with drug molecules via electro-elastic bonds, i.e., ion to ion, in the case of CMC."**

Do you see that, sir?

A. **Yes, I do.**

Q. **And if you turn back to Page 19705, sir, do you see there are two tables? And there is some language between the two tables. Do you see that?**

A. **Yes.**

Q. **And a CMC is a polymer. Correct, sir?**

A. **It is, yes.**

Q. **And do you see here in that right-hand column where it says, "Both the polymers and the cyclodextrins form water-soluble complexes with various drug molecules and can**

be used to solubilize drugs"? Do you see that, sir?

A. **I see where it says polymers and cyclodextrins, yes.**

Q. **Again, CMC is a polymer. And as we saw in their conclusions, they talked about CMC enhancing solubility. Am I correct, sir?**

A. **In the presence of cyclodextrin, which is a solubility enhancing component here. Let's understand that. You have to deconstruct the paper.**

Q. **Sure. Let's go back. They are just talking about CMC, if we look at that last Page 19707?**

A. **You need to read the full paper. This is about the solubility with cyclodextrins.**

Q. **I am reading what it says. Am I reading it wrong when it says, "In our study, the addition of a very small amount, 0.25 percent weight per volume of PVP, CMC, or HPMC, resulted in a significant increase in the aqueous solubility of most of the drugs tested"?**

Did I read that accurately, sir?

A. **You read that accurately, yes.**

Q. **Thank you, sir.**

And if we go back to 19705, looking at the right-hand column this time, it says, "By comparing the solubility of the drugs in water with that in aqueous 05, 25-percent solution of the polymers in Tables 2 and 3, it can be seen that the polymers possess a significant

solubilizing effect themselves."

Correct?

A. **That's what it says.**

Q. **So it says the polymers themselves. Am I correct, sir? Did I read that accurately?**

A. **You read it accurately. In comparison, Table 2 says on cyclodextrin. Let's understand what this means.**

Q. **The authors said the polymers themselves. Am I correct, sir?**

A. **That's what they wrote down there. But that's all pulling it out of context.**

Q. **Thank you.**

THE COURT: Doctor, the language earlier, highlighted to you on Page 707, seems to be written in the dysjunctive. Is that significant to you, when it says "in our study a very small amount," and there is a parenthetic, "of PVP, CMC, or HPMC," is that of significance?

THE WITNESS: I am sorry, sir. What was the question?

THE COURT: You are the only witness, Doctor.

Is it significant to you that the author of this article writes dysjunctively in that sentence?

THE WITNESS: No. They could even put a whole litany of other polymers there. This is a study with cyclodextrin, which is solubilizing.

THE COURT: Okay.

BY MR. BREISBLATT:

Q. **Will you look a Table 2 on Page AGN 0219704.**

A. **Table 2, 704, yes, I have that.**

Q. **Am I correct, as we look at this, it says Table 2, "Effective addition of 0.25 weight per volume CMC to aqueous ten percent"?**

And what they did is -- and correct me if I am wrong -- the authors did more than just test CMC with cyclodextrin. In fact, they tested it in pure water. That is Column 1. Correct?

A. **Well, I would have to read the whole paper --**

Q. **Sir --**

A. **Are you talking about --**

THE COURT: Let him finish, counsel.

BY MR. BREISBLATT:

Q. **Go ahead.**

A. **I have to look at the superscript there. It says solubility in pure water, yes.**

Q. **So we are in agreement, sir. Column 1, they actually tested the CMC in pure water, didn't they?**

A. **Yes. I don't know what the pure water -- normally it is an acidic pH. There is no control over pH here. I have to review the whole paper and understand what the observations are from these scientists.**

Q. **So they tested it in pure water, and then next they tested it in aqueous .25 weight per volume solution of the polymer. So they actually looked at CMC separate than cyclodextrin, didn't they, sir?**

A. **It appears that way, but you would have to again investigate what type of systems they were looking at.**

May I add another comment?

THE COURT: There is not another question on the floor. Ms. Brooks will have an opportunity to ask you additional questions.

THE WITNESS: Thank you, Your Honor.

BY MR. BREISBLATT:

Q. **Let's go to DM2 and Purite. Am I correct, sir, that all of the words under the word Purite would include Purite? Am I correct?**

A. **Yes.**

Q. **Now, you didn't write your patent application, it was a lawyer who helped you with that. Is that correct, sir?**

A. **Correct.**

Q. **Dr. Olejnik, do you have in front of you the book that was handed to you by your counsel yesterday?**

A. **Yes, I do.**

Q. **I would like to direct your attention to the declaration in that, the last page?**

THE COURT: Which exhibit is that, counsel?

MR. BREISBLATT: JTX-00008.

Does the Court have it?

THE COURT: I don't.

BY MR. BREISBLATT:

Q. **Dr. Olejnik, am I correct that this declaration was prepared for you by a lawyer?**

A. **It was submitted in by a lawyer. I was involved in the wording.**

Q. **When you prepared Paragraph 7, was it your decision or the lawyer's decision not to tell them about Refresh Tears?**

A. **I don't remember.**

Q. **So you don't recall whether it was your decision or the lawyer's decision not to mention Refresh Tears then?**

A. **I can't say either way.**

Q. **And you didn't mention at all in Paragraph 7 that Refresh Tears was meant to stay on the eye, did you?**

A. **No, I didn't say that in here, no.**

Q. **And you didn't tell them that Refresh Tears contained CMC?**

A. **No.**

Q. **So the Patent Office never had the opportunity to look at whether it would have been obvious, the combination of Refresh Tears and brimonidine tartrate, did they?**

A. **I don't know.**

Q. **Well, you never told them about Refresh Tears, did**

you?

A. That is correct.

Q. Doctor, you were also shown JTX-054, and this is I guess the one document that didn't make it into your book that made it into all the others.

A. It's in here now, by some magical event.

Q. I think it's called the hole puncher.

A. This is JTX-054. Right?

Q. Correct. It is a memorandum dated June 9, 1998 that you visited with your counsel about. Do you recall that?

A. Could you repeat that question?

Q. Sure. You visited -- you discussed this document with your counsel yesterday. Correct?

A. Yes.

Q. And one of the portions that you discussed with your counsel dealt with Page AGN 0199977?

A. I believe so, yes.

Q. And there was this discussion about an assessment and prediction submitted by an external advisory panel of experts. Do you recall that discussion?

A. Yes.

Q. Now, that advisory panel of experts was there to review the concept of making a product that would only have to be applied maybe once a week or once a month. Am I correct?

A. **No.**

Q. **Are you saying that counsel was there to review the combination of brimonidine tartrate and Refresh Tears?**

A. **It wasn't reviewing brimonidine-Refresh Tears. It was reviewing the composition, looking at our ability to reduce dosing twice a day, doing a shift in pharmacokinetic peaks, as well as assessing other opportunities.**

Q. **In fact, this group came to Allergan, and their focus was on trying to establish an improved dosing regimen of brimonidine going beyond the repeated dosing on a daily basis to something that was extended over days, weeks, and months. Correct?**

A. **Where were you reading from?**

Q. **I am just asking, sir, isn't that what it was?**

A. **It was reviewing the overarching aspects of the project and what we could and could not achieve.**

Q. **Let me see if I can refresh your recollection, sir.**

Do you still have what counsel for Exela gave you up there, that very large book?

A. **The muscle-building book?**

Q. **Yeah. Can you find your deposition from your second day? And let me direct you to Page 75 of it.**

A. **Page 75?**

Q. **Correct. And I also have it up on the big screen if you are having trouble finding it.**

A. **Okay, Page 75. I keep going to Mr. Benson's deposition. I apologize.**

Q. **It would be the second day, sir.**

A. **I have that.**

Q. **And do you recall Mr. Boggs asked you, "What do you recall about this external advisory panel of experts that's referred to in the penultimate paragraph?**

"Answer: This was a group, and I don't remember when they came to Allergan, the focus was on, again, trying to establish an improved dosing regimen of brimonidine going beyond the repeated dosing on a daily basis to something that was extended over days, weeks, months."

A. **That's correct.**

Q. **"So a group of consultants that were skilled in their specific area of expertise as well as an understanding of ocular drug delivery systems were brought together to debate and discuss."**

Is that correct?

A. **Yes.**

Q. **Then you went on, then you were questioned, "What is this that's being referred to there?"**

And you said, "To achieve something that went beyond once a day that would be once a week, once a month?

A. **That's correct.**

Q. **Not whether you could combine brimonidine tartrate and**

Refresh Tears. Am I correct, sir?

A. **Well, that's what our objective was. It doesn't mean to say we didn't have these other discussions. When you have a panel of experts, you are paying them good money and you like to get information out of them.**

Q. **The panel of experts did not review the combination of Refresh Tears and brimonidine tartrate, did they, sir?**

A. **No.**

Q. **Thank you.**

Let me take you to DTX-057.

Dr. Olejnik, do you have DTX-057 in front of you?

A. **Yes, I do.**

Q. **And do you see the date on it? If we go up to the top, this was from that International Journal of Pharmaceutics, and this time it's got a 1996 date. Am I correct?**

A. **Yes, you are.**

Q. **Again, that is prior to the date you claim for your invention. Am I correct?**

A. **That is correct.**

Q. **And, again, you believe that your invention was that CMC would enhance solubility. Am I correct?**

A. **Yes, you are correct.**

Q. **Why don't we look at the very first paragraph on the**

left side of the first page?

Do you see where it says, "Almost 40 years ago, Takoru Higuchi and coworkers investigated interactions of various drugs with a number of water-soluble polymers, i.e., polyethylene glycols, polypropylene glycols, polyvinyl pyrrolidone and carboxymethylcellulose"?

Do you see that?

A. **I see that, yes.**

Q. **Do you see where he then goes on to say, "In aqueous solutions they frequently observed notable increase in drug solubility due to the formulation of water-soluble drug-polymer complexes"?**

Did I state that right?

A. **Yes, you did.**

Q. **And Refresh Tears is an aqueous solution, isn't it, sir?**

A. **It's an aqueous solution. The sentence you read, "Also sometimes phase separation was observed."**

Q. **Why don't we look at AGN 0219697. And we are looking at the right-hand column.**

A. **Okay.**

Q. **I am looking at the sentence that begins, "Previously," and going down to Lawson, et al., 1994?**

A. **Okay.**

Q. **And do you see where it says, "Previously, we have**

shown that additions of 0.25 milliliter per volume PVP mol. to water results in an average of 64-percent increase in the aqueous solubility of nine different drugs and the addition of 0.25 weight per volume of carboxymethylcellulose results in an average of a 53-percent increase in the aqueous solubility of 16 different drugs"?

Did I read that correctly?

A. **For the most part, yes.**

Q. **Sir, how much CMC do you use in your brimonidine tartrate product?**

A. **It's .5 percent.**

Q. **So that's more than .25. Am I correct?**

A. **That's more than .25. But equally, you have to look at the way these scientists had prepared the solutions, particularly as I look at this paper, they use autoclaving, they increase the temperature, they create a saturated solution. You are actually forcing more into solution. So those observations can be deemed incorrect as you begin to review it further.**

Q. **Am I correct, sir, the document says, "Carboxymethylcellulose resulted in an average of a 53-percent increase in the aqueous solubility of 16 different drugs"?**

Am I correct?

A. **Based on the methodologies they used, which, again,**

are subject to critique. But, yes.

Q. **And this was published in a refereed journal, isn't it?**

A. **It's a refereed journal. It's -- no, it's not a research article. It's essentially a communication. I don't know to what extent it gets refereed.**

Q. **It is telling people skilled in the art about CMC and its solubility enhancing components?**

A. **No, not from my perspective it's not.**

Q. **And you have reviewed this article before, haven't you?**

A. **I have seen it with legal.**

Q. **When you say you have seen it with legal, I don't understand that. What do you mean?**

MS. BROOKS: Your Honor, I would ask that Dr. Olejnik not disclose communications that he has had with counsel.

THE COURT: He can explain what he means by that.

MS. BROOKS: Yes. Thank you.

THE WITNESS: Well, I sat down with Fish & Richardson, when I was shown this paper.

BY MR. BREISBLATT:

Q. **That's when you were preparing for what, your deposition or for your legal testimony here?**

MS. BROOKS: Your Honor, I think --

THE COURT: No. He can answer that question.

THE WITNESS: I think it's for the case here, I believe.

BY MR. BREISBLATT:

Q. **So in preparation for your trial, you finally reviewed this article. Am I correct?**

A. **I didn't review it in full, no.**

Q. **And you went over it with the lawyers. Am I correct?**

A. **I don't remember to what extent. It was very brief.**

Q. **So you never saw this article before you did your work on your project, did you?**

A. **I don't remember this article. I see so many articles. I might have. I don't remember.**

Q. **But one skilled in the art would have seen it before your invention. Am I right?**

A. **Perhaps.**

Q. **Well, let's look at one more part of this article that you had a chance to review with your lawyers. That's on DTX-057, Page 19697. And we left off with the reference to Lawson. Do you recall that?**

A. **Yes, I do.**

Q. **If we look at the very next sentence, it says, "The solubility studies indicate that a large fraction, e.g., 30 to 50 percent of drug molecules in aqueous polymer solutions**

are bound to the polymers."

That would be the CMC. Am I correct?

A. **Not exactly, because they talk about PVP.**

Q. **But they talk about CMC and CMC is a polymer. Am I right. Sir?**

A. **If I look above, "previously have shown the addition of PVP," polyvinyl pyrrolidone, "results in an average of" --**

Q. **Do you see where it also says --**

A. **It says 53 and indicated a large fraction, for example, 30, 50. You could infer that it is CMC.**

Q. **It goes on and says, "This will not only affect the aqueous solubility of the drugs but also various other physiochemical properties of the drugs and their availability in aqueous drug formulations."**

Did I read that accurately, sir?

A. **Yes, you did.**

Q. **And this, again, is from 1996, prior to your invention. Am I right, sir?**

A. **That is correct.**

MR. BREISBLATT: Your Honor, may I have a moment to make sure I have done everything? And I should be done.

(Pause.)

BY MR. BREISBLATT:

Q. **Now, yesterday, you indicated that you thought that**

your invention was the first time Purite was used with an active ingredient. Am I correct?

A. **Yes.**

Q. **But Purite had been being used in Refresh Tears from 1997, for two years before, or for about a year before your invention. Am I correct?**

A. **Yes.**

Q. **And it was being put into the human eye on a daily basis throughout at least the United States and Canada. Am I correct?**

A. **Correct, in patients.**

Q. **In fact, it was so safe for use that the FDA was allowing it to be sold over the counter. Am I right?**

A. **It's an over-the-counter product.**

Q. **And one skilled in the art would have known, just from that, that the Purite in the human eye and the CMC in the human eye wasn't going to be an issue. Am I correct?**

A. **Well, CMC is a drug listed, recognized as a safe excipient, yes.**

Q. **And Alphagan with brimonidine tartrate, .2 percent, had been being sold by your company for a number of years before July of 1997. Am I correct?**

A. **Again, I don't recall when it was -- I am not good at dates as to when products go into the marketplace.**

Q. **It had been on sale before?**

A. **It would have been on for a number of years, yes.**

Q. **The FDA hadn't pulled it at that time because of safety, had they?**

A. **No, it had not.**

Q. **And one skilled in the art would have known it was safe. Am I right, sir?**

A. **It's safe as a risk-benefit for our adverse events, there is no doubt we have heard. Yes, sir.**

MR. BREISBLATT: No further questions.

THE COURT: Thank you, Mr. Breisblatt.

Ms. Brooks, your redirect.

MS. BROOKS: Thank you, Your Honor.

REDIRECT EXAMINATION

BY MS. BROOKS:

Q. **Dr. Olejnik, just briefly as to the very last question, you were asked whether or not before you combined the brimonidine with the Refresh Tears, the excipients from the Refresh Tears, if Purite had ever been used previously with an active ingredient. Do you recall that?**

A. **Yes, I do.**

Q. **Is there an active ingredient in Refresh Tears?**

A. **No, there is not.**

Q. **What if any concerns did you have of combining Purite with the active ingredient of brimonidine?**

MR. BREISBLATT: Objection. Outside the scope

of cross-examination.

THE COURT: Well, it's a bit. But I am going to permit it.

BY MS. BROOKS:

Q. **If you could just answer that one?**

A. **There is a concern you are using an oxidizing agent and it will and can degrade drug contents.**

Q. **I would like to go back to questions Mr. Boggs asked you yesterday at the end of the day regarding specifically the '834 patent. So if you could find that in your notebook, please.**

A. **That's JTX-004?**

Q. **I believe that's correct, Dr. Olejnik. Yes, it is, it is JTX-004. The '834 patent. Do you have that in front of you?**

A. **Yes, I do.**

Q. **If we could go, please, to Claim 1 that Mr. Boggs was asking you questions about, and that is at Column 16. Does Claim 1 claim "a therapeutically effectively aqueous ophthalmic composition" -- and let's stop right there. Is that one part of Claim 1?**

A. **Yes.**

Q. **Mr. Boggs was asking you to look through the patent and see where this language may appear. Do you recall that yesterday afternoon?**

A. **Yes, I do.**

Q. **Let's go through, if we could, and let's start with the term ophthalmic. Do you see where that appears in Claim 1, right there on the screen?**

A. **Yes, I do.**

Q. **Let's go to the Elmo now if we could, because I think I can do it a little faster this way. I am going to turn, Dr. Olejnik, to Column 1, and specifically, I am going to go to Line 58. I am going to get myself oriented here on the Elmo so I can do this correctly.**

Looking at Column 1, starting at Line 56, I guess it says, under summary of the invention, do you see that, Dr. Olejnik?

A. **Yes, I do.**

Q. **And does it say here, "The present compositions, containing certain materials, which are effective in at least aiding or assisting in solubilizing the alpha-2 adrenergic agonist components in the compositions, and preferably in environments to which compositions are administered or introduced, for example, biological environments, such as the human eye."**

Did I read that correctly?

A. **Yes, you did.**

Q. **What is the field of ophthalmics related to? What part of the body?**

A. **The eye.**

Q. **Now let's turn, if we could, to Column 3, going to Line 19.**

A. **Column 3, did you say?**

Q. **Yes. Column 3, going to Line 19. If you need help, it's also up on the screen. Does it say here, "The compositions include carrier components, for example, aqueous liquid carrier components. In one embodiment, the compositions have pH's of about 7 or greater, preferably about 7 to about 9, and are ophthalmically acceptable."**

Did I read that correctly?

A. **Yes, you did.**

Q. **Again, when one says ophthalmic, what part of the body is one referring to?**

A. **That's the eye.**

Q. **Let's go to Column 3 again, moving down to Line 37, "The compositions do not have deleterious or toxic properties which could harm the eye of the human."**

Did I get that part correct, Dr. Olejnik? That's Column 3 at approximately Line 37.

A. **That's correct. I would have said deleterious, but that's correct.**

Q. **Deleterious?**

A. **That's what I would say. Maybe it's the vernacular.**

Q. **My apologies. I am sure I mispronounced it.**

Let's go to Column 6, Line 30. Does it say at Column 6, Line 30, "Furthermore, the polyanionic component is preferably ophthalmically acceptable at the concentrations used"?

Again, Dr. Olejnik, if it assists you I have it up on the screen highlighted.

A. **The polyanionic component, yes.**

Q. **Again, did I read that correctly?**

A. **Yes.**

Q. **Let's look at Column 8, Line 41. We will start at Line 40: "Since the polyanionic components are preferably ophthalmically acceptable, it is preferred that the metal associated with the unionized polyanionic component be ophthalmically acceptable in the concentrations used."**

A. **In the concentrations used, yes.**

Q. **And is that at Column 8, starting at Line 40?**

A. **Yes.**

Q. **Let's turn to Column 11, specifically, we will go to Line, approximately Line 6.**

A. **I am sorry. Magically, it has disappeared.**

Q. **That page is absent from mine as well.**

MS. BROOKS: I am sorry, Your Honor. I have lots of extra copies here. If I might have a moment.

THE COURT: It's Bates 219, are the last three numbers.

MS. BROOKS: If I might approach, Your Honor, with that page?

THE COURT: Do we have another one?

MS. BROOKS: Yes.

If I might approach the witness, Your Honor?

THE COURT: Yes, you can do that.

MS. BROOKS: My apologies, Your Honor. I noticed it was missing from mine last night, but I thought it was me, that I just lost it.

BY MS. BROOKS:

Q. **Turn now, Dr. Olejnik, to Column 11, starting at Line 6, does it say, "The liquid medium preferably has an ophthalmically acceptable tonicity level"?**

A. **Yes.**

Q. **And now going to Column 11, Line 34, does it say, "Any suitable ophthalmically acceptable tonicity component or components may be employed"?**

A. **That's what it says, yes.**

Q. **And just a few more places. Let's turn to Column 13. Mr. Boggs asked you several questions about Example 1, which is at Column 13 in the '834 patent. This is the example that results in eventually the data in Table 2. Do you recall that, Dr. Olejnik?**

A. **Yes, I do.**

Q. **And also, there is data contained in Table 1 which is**

the formulation that is used in Example 1.

A. **I see that.**

Q. **Did I get that correct?**

A. **Yes.**

Q. **Let's see what formulation is actually being used in Example 1. If we look at Column 13, at Line 18, what is that formulation called?**

A. **Ophthalmic Solution.**

Q. **And if we look at Table 1 in Column 14, what is that formulation called?**

A. **Ophthalmic Solution.**

Q. **If we look at Column 2 -- I am sorry, Column 14 at Table 2, what is that formulation called?**

A. **Ophthalmic Solution.**

Q. **As one of skill in the art, Dr. Olejnik, having just gone through these ten, I think, or 11 examples, from reading this, would you have any indication that this patent, including the specification, was discussing ophthalmic solutions?**

MR. BREISBLATT: Objection, Your Honor. Calling for an opinion.

THE COURT: Let me see counsel at sidebar.

(The following took place at sidebar.)

THE COURT: What is your reaction to that objection?

MS. BROOKS: That Mr. Boggs cross-examined Dr. Olejnik about what he, as one skilled in the art, would or would not have known from the specification as to what this invention was and whether or not the invention was supported by the specification.

THE COURT: Regardless of the technical accuracy of your objection, isn't that true? Didn't you explore that?

MR. BREISBLATT: That was Mr. Boggs.

THE COURT: You made the objection so you answer the question.

MR. BREISBLATT: My objection is simply based on the fact that she can't ask for an opinion. In other words, he wasn't proffered as an expert.

THE COURT: I got all that. Answer my question. Isn't it fair, given the nature of the cross? We are about fairness here, in addition to technical rules.

MR. BREISBLATT: I --

THE COURT: Overruled.

(End of sidebar conference.)

THE COURT: The objection is overruled.

(Question read as follows:

"Question: As one of skill in the art, Dr. Olejnik, having just gone through these ten, I think, or 11 examples, from reading this, would you have any indication

that this patent, including the specification, was discussing ophthalmic solutions?")

THE WITNESS: Discussing ophthalmic solutions.

BY MS. BROOKS:

Q. **Let's move on to the term -- we are still with Claim 1 of the '834 patent. It not only refers to ophthalmic, it refers to therapeutically effective. Let's go back to Column 3 if we could. And specifically, at Line 12, at Line 12 at Column 3, does the specification disclose that, "This interaction," referring to the above sentence regarding the polyanionic component, "This interaction preferably is sufficient to render the alpha-2-adrenergic components substantially completely soluble at therapeutically effective concentrations"?**

Did I read that correctly, Dr. Olejnik?

A. **Yes, you did.**

Q. **Is that contained in the specification, specifically, at Column 3, starting at Line 11?**

A. **Yes.**

Q. **Let's stay with Column 3 and go to Line 26, or actually, we will begin with Line 24: "In a preferred embodiment, a composition is provided which includes an alpha-2-adrenergic agonist component in an amount effective to provide at least one therapeutic benefit to a patient to whom the composition is administered."**

Did I read that correctly, Dr. Olejnik?

A. **Yes, you did.**

Q. **Is that contained in the specification of the '834 patent that Mr. Boggs discussed with you yesterday?**

A. **Yes.**

Q. **Now let's turn to Column 13. And we are looking at Example 1, at Line 19, "It will be understood that concentrations of adrenergic agonists other than .5 percent may be used so long as they have therapeutic activity."**

Did I get that correct, Dr. Olejnik?

A. **Yes.**

Q. **Now, again, as one of skill in the art, having looked at these three examples within the specification referring to either therapeutic benefit or therapeutic activity, would you have had an understanding as to whether or not this patent dealt with a composition that was therapeutic?**

A. **Yes, it would.**

Q. **Now, this particular one also talks about that the adrenergic agonists -- let me ask you, again, is brimonidine an alpha-2-adrenergic agonist?**

A. **It's an adrenergic agonist. It's an alpha-2, yes.**

Q. **And Claim 1 of the '834 patent is specifically claiming the use of brimonidine of up to about .15 percent?**

A. **Correct.**

Q. **Is up to about .15 percent a concentration other than**

.5 percent?

A. **Yes.**

Q. **Let's see where else we might be able to find the .15 percent. If we go to Column 11, and specifically, let's start with Line 3, "The aqueous liquid carrier preferably has a pH in the range of about 6 to about 9 or about 10, more preferably about 6 to about 8, and still more preferably about 7.5."**

Did I read that correctly, Dr. Olejnik?

A. **Yes.**

Q. **Is that contained in the specification of the '834 patent, starting at Line 4?**

A. **Yes.**

Q. **Now, let's look at this particular, the most preferable pH described here, 7.5. If we could turn to Table 4, which appears in Column 15, do you recall what Table 4 at Column 15 reflects?**

A. **Yes. It's a solubility pH profile of brimonidine tartrate in the presence of CMC and without CMC.**

Q. **And if we look at the pH here of about 7.5, in fact, it's 7.566. Can you tell me what amount of brimonidine is in full solution at the preferable pH of 7.5?**

A. **At the CMC at 0.5 percent, it's about .15.**

Q. **In fact, is it .1451?**

A. **Correct.**

Q. **Is that up to about .15 percent?**

A. **Yes, it is.**

Q. **Now, let's move onto the second element of that claim. Does it talk about having a pH of up to about 7.0 or greater?**

A. **Yes.**

Q. **And do you recall Mr. Boggs asking you whether that appeared anywhere in the specification?**

A. **Yes.**

Q. **Now, if we could, let's turn to Column 3. I believe I have already highlighted this for another purpose, which was for the "ophthalmically" purpose. But do we see at Column 3 starting at Line 19, where it says, "In one embodiment the compositions have pH's of about 7 or greater"?**

A. **Yes.**

Q. **Preferably, about 7 to about 9?**

A. **Yes.**

Q. **And if we could go to Column 4, Line 29, does it discuss how the alpha-2-adrenergic components have increased solubility in the present compositions at pH's in the range of about 7 to about 10?**

A. **Yes.**

Q. **And if we go to Column 4, Line 47, does your specification for the '834 patent describe, again, how preferably the biological environments into which the**

present compositions are introduced have pH's ranging from about 7 to about 9?

A. **Yes.**

Q. **And if we go to Column 7, starting at Line 10, does it describe how, "In another embodiment, the polyanionic components include anionic polysaccharides which tend to exist in ionized forms at higher pH's, for example, pH's of about 7 or higher"?**

A. **Yes.**

Q. **And is that --**

THE COURT: Ms. Brooks, we will have to leave it there. We will resume, unless you are otherwise notified, between 2 and 2:15.

MS. BROOKS: Thank you, Your Honor.

(Recess taken.)

- - -

THE COURT: Please be seated. Hopefully, there won't be anymore interruptions of the type I have made today. But sometimes we have matters off the Bench. And that's what happens.

Ms. Brooks.

MS. BROOKS: Thank you, Your Honor.

BY MS. BROOKS:

Q. **Dr. Olejnik, I believe we were working with the '834 patent that Mr. Boggs had asked you about yesterday. And if**

you could go back to the '834 patent, which is JTX-004, and let's go back and look, if we could, at Claim 1.

Earlier, we have already talked about where in the specification we could find the term "therapeutically effective," where we could find the term "ophthalmic," where we could find the "up to about .15 percent," where we could find the "pH of up to about 7.0 or greater."

I am not going to repeat all of that.

The last one talks about the brimonidine being soluble in the composition at about 21 degrees Centigrade.

What is 21 degrees Centigrade? What is the significance of that?

A. It's room temperature.

Q. Room temperature?

A. Yes.

Q. Did your work that is disclosed in the '834 patent and the other three patents at issue discuss the solubility of brimonidine at room temperature?

A. Yes.

Q. Now, Mr. Boggs also asked you whether or not in the '834 patent, in the specification, whether the terms "glaucoma" or even "intraocular pressure" were mentioned.

Do you remember him asking you that?

A. Yes, I do.

Q. If you look at Claim 1, does it limit this

therapeutically effective aqueous ophthalmic composition to be one for the treatment of glaucoma?

A. **It would, yes.**

Q. **Does it limit it to that? In other words --**

A. **No.**

Q. **-- is it saying a therapeutically effective aqueous ophthalmic composition for the treatment of glaucoma?**

A. **Not limiting it to glaucoma. There could be other indications, as I mentioned yesterday.**

Q. **Let's see, though, whether or not within the art and the patent there is a discussion about the use of brimonidine tartrate for lowering intraocular pressure.**

First of all, at the time that you applied for the patents at issue, after your development of Alphagan P, was Alphagan already on the market?

A. **Yes, it was.**

Q. **So, was it known that the use of brimonidine tartrate could lower intraocular pressure?**

A. **Yes.**

Q. **Now, if we could pull up ADX-3, and, specifically, the big eye that is up in the upper right-hand corner?**

Looking at this, Dr. Olejnik, do you see right here where it says "cornea"?

A. **Yes.**

Q. **And could you show the Court, where is the cornea**

located on this side-view of the eye?

A. **Do I draw on this?**

Q. **I can draw on it if you would like. Right there. We are looking at essentially the cornea. Is that right?**

A. **Yes, correct.**

Q. **When the brimonidine is put into the eye, what membrane does it have to permeate in order to get into the eye to lower intraocular pressure?**

A. **Well, it would be first epithelium of the cornea.**

Q. **Let's go to the patent, then, and see if we can find anything specifically about cornea. If we look at Column 4, and go to Line 47, and I am going to go back to the Elmo for this, and if we look at Column 4, at line 47, after we have "the present compositions are introduced having pH's ranging from about 7 to about 9," does it then say, "For example, a composition comprising a SEC and an alpha-2-adrenergic agonist component may be administered to the cornea of an eye, which has a pH of about 7, wherein the alpha-2-adrenergic agonist component is substantially solubilized at the administered area"?**

A. **Yes.**

Q. **What is the significance, in relation to your invention, as disclosed in the patent, what is the significance of the fact that the cornea of the eye has a pH of about 7?**

A. **It's a physiological pH and you want to ensure the non-ionized form of the drug is available for it to penetrate through the corneal epithelium.**

Q. **Now if we could turn to Column 6, at Line 11, does it disclose, "In another embodiment, adrenergic compounds are substantially unionized in the environment to which they are administered, for example, the cornea"?**

A. **Yes.**

Q. **Is that yet another discussion of your invention as it pertains to the cornea?**

A. **Yes.**

Q. **Now, if we go to Column 16, and we go to Line 29 through 31, does it say, "CMC is also effective to solubilize brimonidine tartrate in a biological environment, for example, the biological environment of the cornea"?**

A. **That's what it says, yes.**

Q. **Again, why is it important for the brimonidine, the CMC to solubilize the brimonidine tartrate in the biological environment of the cornea?**

A. **To make it bioavailable for the non-ionized form to remain in solution for it to have effect, to penetrate through the cornea.**

Q. **Thank you.**

Let's go back, just to finish up on this written description issue, back to ADX-3 and show the large eye

again.

Dr. Olejnik, right here, it says -- I am never any good at this.

A. Ciliary.

Q. "Ciliary body and muscle." Do you know what that is?

A. Yes.

Q. What is that?

A. It's a muscle through which the aqueous humor is generated, made. It goes into the anterior chamber of the eye.

Q. Is one of the problems in glaucoma the fact that the aqueous humor is not adequately going through the ciliary muscle?

A. Through the ciliary muscles and the canals of schlem, yes.

Q. If we could go back to the patent, specifically, Column 5, Line 21. Actually, starting up above, so we can put this in context, at Line 18, does the specification read, "Additionally, they also work on alpha-2-adrenergic receptors post synaptically, inhibiting beta adrenergic, receptor stimulated formulation of cyclic AMP, which contributes to the relaxation of the ciliary muscle, in addition to the effects of postsynaptic alpha-2-adrenergic receptors on the other intracellular pathways."

Did I read that correctly?

A. **Yes, it's cyclic AMP, but yes.**

THE COURT: Ms. Brooks, I missed the column. What column was that?

MS. BROOKS: Column 5, Line 18.

BY MS. BROOKS:

Q. **I mispronounced cyclic?**

A. **Cyclic. The cyclical and the cyclical.**

Q. **So is this part of the specification talking about the relaxation of the ciliary muscle?**

A. **Yes, it is.**

Q. **And, again, how is the ciliary muscle involved in the formation or creation of glaucoma?**

A. **It is important for the formation of the aqueous humor that is building up in the anterior chamber to have an effect on intraocular pressure.**

Q. **If we could go back to ADX-3 one more time, we have heard, Dr. Olejnik, and I actually mentioned in opening statement, that what glaucoma does is the increase of intraocular pressure causes pressure in the eye which can damage the optic nerve. Is that your understanding, also?**

A. **That is correct, if it goes untreated.**

Q. **This is the optic nerve right here?**

A. **Yes.**

Q. **Now, let's go back to the patent one more time, still at Column 5, and look at, starting at Line 28, does it**

disclose in the specifications how "alpha-2-adrenergic agonists also include compounds that have neuroprotective activity"?

A. **Yes.**

Q. **What is your understanding of what that is disclosing in the specification?**

A. **It is disclosing to protect the optic nerve, the renal segmental epithelium, the posterior chamber of the eye, protecting eyesight.**

Q. **Thank you.**

Let's move now from Mr. Boggs' questioning of you yesterday to Mr. Breisblatt's questioning of you today.

If you could go to PTX-295 that Mr. Breisblatt asked you about, I know you have a lot of stuff there in front of you, so take your time and let me know when you find it. It is the brimonidine's Purite Phase 3 investigator meeting?

A. **I have it.**

Q. **First of all, was this written by you?**

A. **No.**

Q. **Who was it written by?**

A. **By Dr. Joe Vehige.**

Q. **Who is Dr. Vehige?**

A. **He is an optometrist. He was in the clinical group, I believe, at the time this was written.**

Q. **Is Dr. Vehige a formulator?**

A. **No.**

Q. **Did Dr. Vehige assist you in the formulation of Alphagan P?**

A. **No.**

Q. **Did he assist Dr. Kerslake in the formulation of Alphagan P?**

A. **No.**

Q. **Now, if we turn to Bates No. 292359 within that document, it's the Refresh Tears formulation.**

Do you recall Mr. Breisblatt asking you about the Refresh Tears formulation this morning?

A. **Yes, I do.**

Q. **Now, what is the pH of the Refresh Tears formulation?**

A. **7.7.**

Q. **And if we look at sodium chloride within the Refresh Tears formulation, what is the amount of sodium chloride?**

A. **.62 percent.**

Q. **And do you see anywhere within the Refresh Tears formulation sodium borate?**

A. **No, I do not.**

Q. **What is sodium borate?**

A. **That's salt of boric acid, which is also used for buffering purposes.**

Q. **If we can go to the next page, which is the**

brimonidine-Purite formula comparison.

Again, did you prepare this particular chart?

A. **No, I did not.**

Q. **Did you ever make a comparison specifically between what was in the Refresh Tears formulation and what was in the brimonidine-Purite formulation?**

A. **No, I did not.**

Q. **Did you have any reason to do that?**

A. **No.**

Q. **Did you know what was in the brimonidine-Purite formulation because you were one of the individuals working on the formulation?**

A. **I knew what was in the brimonidine-Purite formulation, yes.**

Q. **And what is the pH of the brimonidine-Purite formulation?**

A. **7.3 here.**

Q. **Does that differ in any way from the pH of the Refresh Tears formulation?**

A. **Yes, it does.**

Q. **In what way?**

A. **It's lower.**

Q. **Is there anything in this chart that would account, to you as a formulator, account for the lower formulation of -- lower pH of brimonidine-Purite compared to the Refresh Tears**

formulation?

A. **Yes. I am trying to bring it into a more physiological pH range and handling solubility challenges with the brimonidine tartrate.**

Q. **Would you have been able to do that if you simply did, as Mr. Breisblatt suggested, and grabbed a bottle of Refresh Tears off the shelf and grabbed the brimonidine tartrate and mixed them together?**

A. **No. My concern is it would have precipitated out of the brimonidine tartrate at the high pH.**

Q. **Is there sodium borate in the brimonidine-Purite formulation?**

A. **Yes, there is.**

Q. **I believe we just saw that it is not in the Refresh Tears. Is that right?**

A. **That's correct.**

Q. **And what is the amount of sodium chloride in the brimonidine-Purite formulation?**

A. **.58 percent.**

Q. **Is that lower than the .62 percent that is in the Refresh Tears formulation?**

A. **Yes, it is.**

Q. **Dr. Olejnik, do you recall at any time anyone, either yourself or anyone under your supervision, simply taking the Refresh Tears formulation, putting some brimonidine in it,**

mixing them together, and calling it Alphagan polypropylene?

A. **I am not aware of any, no.**

Q. **Did the data that we just looked at indicate that that is what happened?**

A. **No.**

Q. **What does it indicate?**

A. **It indicates that it's a different formulation to Refresh Tears. What it indicates are similarities in terms of the excipients that were being used.**

Q. **Now, if we can go to, please, JTX-080. That is entries from Mr. Padilla's lab notebook that Mr. Breisblatt showed you. And, specifically, if we can go to 66787, if we could blow up, please, that part. Thank you.**

Mr. Breisblatt simply asked you about the very first line, said, we assume that this says "purpose" and it's just cut off, "to formulate a new brimonidine formula using the Refresh Tears base."

Do you recall him asking you about that?

A. **Yes, I do.**

Q. **There is more underneath. There is actual bullet points underneath that. Right?**

A. **Yes.**

Q. **What are the bullets points?**

A. **Changes will promote a high viscosity with CMC to promote a retention time. A borate buffer from pH 7.0 to**

7.5. Purite or chlorite is a more gentle preservative and electrically balanced buffer.

Q. **The borate buffer from 7.0 to 7.5, if the Refresh Tears is at 7.7 pH, then what would the borate buffer be placed in there to do?**

A. **It would be placed in there to ensure that the pH 7.7 was maintained.**

Q. **What about the changes will include a higher viscosity CMC, a higher viscosity CMC from what, what CMC is this referring to?**

A. **That would be changes from the CMC that would have been used in Refresh Tears.**

Q. **So, is this an indication whether or not Refresh Tears was simply taken off the shelf, the brimonidine tartrate was added, and that was that? Which way does this indicate?**

A. **It was a different composition.**

Q. **Thank you.**

Now, if we could turn, please, to JTX-043, those were the meeting minutes from the June 1997 time frame.

Do you recall Mr. Breisblatt asking you questions about that?

A. **Yes, I do.**

Q. **I believe he asked you, if I can find the place he talked to you about, I think it was on Page 2, evaluate two formulations of Refresh Purite and one is CMC sodium**

chlorite and one is CMC sodium chlorite with cyclodextrin.

At this point in time when this is written, are these the only formulations, then, that you are now looking at for what will eventually turn into Alphagan P?

A. **I believe that was the case, yes.**

Q. **If we go -- it certainly looks that way if we just look at that page. Is that right, Dr. Olejnik?**

A. **Yes.**

Q. **Which is the only page that Mr. Breisblatt showed you this morning?**

A. **Yes.**

Q. **Let's go, then, to the first page.**

Actually, if we look at the first page, under "Action," right here, "Executive Summary," do you see where it says, "Add to the potential list of formulations the following, self instill, commode, cyclosporin formulation"?

A. **Yes, I see that.**

Q. **Are those, yet, other formulations that are being reviewed during this time period?**

A. **Yes. They are different formulations and different container closure delivery systems as well.**

Q. **If we go to the next action item, "Review the possibility of a carbopol formulation in Self Instill," is that yet another formulation that is still being looked at in the June 97 time frame?**

A. **Yes, it is.**

Q. **Thank you.**

Let's turn to the two papers that Mr. Breisblatt showed you from a Dr. Loftosson.

Do you remember that whole discussion this morning?

A. **Yes, I do.**

Q. **And one of them is DTX-341, that's the Loftosson paper from 1994. Take your time finding it. The other one is DTX-057. That is the Loftosson paper from 1995.**

Do you recall being asked questions about those, Dr. Olejnik, by Mr. Breisblatt?

A. **Yes, I do.**

Q. **As I recall, you said something about what this really taught, the first Loftosson paper, the 1994 paper, was about the use of cyclodextrins as solubility enhancers.**

Did I understand you correctly?

A. **It's the use of cyclodextrins as solubility enhancers, yes.**

Q. **Let's start with the name. What is the name of this paper?**

A. **"The effect of water-soluble polymers on drug-cyclodextrin complexation."**

Q. **Then if we can go to the introduction, which is on the same page, I, could you read for us, or even perhaps**

summarize for us, what this is discussing right here in the introduction when it's talking about how cyclodextrin has a cylindrical shape somewhat hydrophobic center cavity, hydrophilic --

THE COURT: Just let him read it, and he can summarize.

BY MS. BROOKS:

Q. **That would be great. Could you read, actually, the introduction in the first column, going through the second column, ending with a citation to Loftosson, 1991, to yourself, and then explain to us its relationship, what's being described here to what you actually showed us yesterday when you got up at the white board?**

A. **It, again, is basically talking about the hydrophobic center core, that donut, in which you would have a propensity of the more lipophilic moiety to reside in that hydrophobic or non-polar form, which is what cyclodextrin does in a general sense.**

Q. **And, again, I believe we established yesterday that the claims that I showed you, I think of the '873 patent for example, specifically exclude cyclodextrin as an SEC in your invention?**

A. **Yes, it excludes it, yes.**

Q. **Now, do you agree with Dr. Loftoson's description here about how cyclodextrin functions as an SEC?**

A. **I agree with the cyclodextrin as a solubility enhancer. I disagree with some portions of the paper.**

Q. **Let's look at that, the portions of the paper that you disagree with. Let's go right now to Table 2, which is the table that Mr. Breisblatt asked you about. If we could blow up the table.**

Now, first of all, let's look at, because Mr. Breisblatt didn't read this part to you, let's look at what Table 2 is actually describing.

Right underneath Table 2, could you read for us, please, what it says?

A. **"Effects of addition of 0.25 percent weight per volume CMC to aqueous ten percent weight per volume hydroxypropyl beta cyclodextrin M50.6 solution on the HP beta CD solubilization of various drugs."**

Q. **So this right here, this HP beta CD, what does that stand for?**

A. **It's hydroxypropyl beta cyclodextrin.**

Q. **What is Table 2 then telling us about?**

A. **Well, it's telling, you read the table, that the presence of cyclodextrin is enhancing the solubility. And it's enhanced further in the presence of polymers. But you have to understand, when you read papers, particularly myself, I go directly to the methods and materials.**

If you want to understand the methodology, you

have to do that, because you could have erroneous results if you don't understand whether the methods here used were indeed correct.

Q. **Why don't we do that. Let's go, before we do, let's look at the one column that Mr. Breisblatt asked you about, which was Column 2 of the table, but we are going to need the whole table back up if we could. Let's just leave it there. Let's look at Column 2. There is a real small, I think it's a letter "B" next to it. Column 2 is described as solubility in aqueous .25 percent weight per volume solution of the polymer.**

A. **Yes.**

Q. **Is that correct?**

A. **Yes.**

Q. **So, if I am understanding this right and I am reading this chart right, would the first column simply be these active ingredients in water and their solubility?**

A. **They are in water, solubility is not mentioned, pH control, but they are in water.**

Q. **So there is no reference, first of all, to anything about pH in here?**

A. **No.**

Q. **Secondly, these particular active ingredients, are any of them alpha-2-adrenergic agonists?**

A. **No, they are not.**

Q. **Thirdly, when we come to the second column, which is apparently now the non-alpha-2-adrenergic agonists combined with CMC, did you look in the paper as to the methodology for testing the solubility of these non-alpha-2-adrenergic agonists in the presence of CMC?**

A. **Yes. I looked at the methods. That's where I normally go when I read a paper.**

Q. **Right. If we could go back, then, specifically to 2.2, it's on Page 3 of 12, under "Materials and Methods," it has materials and then 2.2 says, "solubility studies."**

Can you explain to the Court how Dr. Loftosson performed the solubility studies that are reflected in Table 2?

MR. BREISBLATT: Your Honor, I have an objection.

THE COURT: It is?

MR. BREISBLATT: The document speaks for itself and this witness has not been listed as an expert. We have an expert. If he wants to talk about what he thinks Dr. Loftosson did, he can. But this witness wasn't part of this experiment. The document speaks for itself.

THE COURT: Sustained.

BY MS. BROOKS:

Q. **Dr. Olejnik, do you know, as one of skill in the art, in looking at this paper, whether or not there was any**

heating of the solutions that were used in the solubility studies?

THE COURT: Let me see counsel.

(The following took place at sidebar.)

THE COURT: I understand what you are trying to do, but I am not sure this is the witness that you should be permitted to do that with. I do understand.

While I have you at sidebar, obviously, he is a key witness, I don't normally entertain an additional round of cross, but I am offering that in this instance, Mr. Breisblatt. If you want to take me up on that, I will let you have the last word. It is an important issue. I want to be clear that I am clear about it.

MR. BOGGS: Your Honor, may I have cross?

THE COURT: You may. I didn't mean to leave you out, Mr. Boggs.

(End of sidebar conference.)

BY MS. BROOKS:

Q. **Dr. Olejnik, let me ask you about your own solubility studies and the ones that were done by Allergan in the formulation of Alphagan P.**

Was there any heating of the formulas performed before studying the solubility of the brimonidine?

MR. BREISBLATT: Your Honor, my objection is it is outside the scope of cross.

THE COURT: I will permit some leading here.

MS. BROOKS: Thank you, Your Honor.

THE WITNESS: They're all done at room temperature. And you wouldn't be doing solubility studies, particularly heating, sonicating, raising the temperature at 120 degrees, which is well above the boiling point of water, you create supersaturated systems. There is more drug in there than actually occurs under normal conditions.

So all of our studies are done under normal conditions.

Q. **Let's turn briefly, then, to the 1995 paper that Mr. Breisblatt asked you about. I believe he read to you, it's DTX-057. First of all, let's just turn very quickly to Table 1, which shows the studies or what was being studied in this paper.**

Is CMC being studied at all in this 1995 paper?

A. **No, it's not. Again, when concentrations are looked at, one has to use validated analytical methods. And the problem with these papers, which I have a problem with a lot of research papers, they don't follow the validation systems that the FDA Guides document provides. That is important to understand.**

Q. **Was Dr. Loftosson, in this particular paper, the 1995 one, was he looking at hydroxypropyl methylcellulose and polyvinyl pyrrolidine, also known as HPMC and PVP?**

A. **Yes.**

Q. **Are either of those carboxymethylcellulose?**

A. **No, they are not.**

Q. **Do they have different structures than carboxymethylcellulose?**

A. **Different structures, different charges.**

Q. **Different charges?**

A. **Yes. They are nonionic.**

Q. **And if we could go back to the first page, I believe Mr. Breisblatt pointed out that this was based on some very early work. If we could go down to the bottom of the first column, it says, "Almost 40 years ago, Tekura Taguchi and coworkers invented interactions of various drugs with a number of water-soluble polymers," and, there, one of the polymers listed is carboxymethylcellulose?**

Did I get that correct?

A. **Yes, you did.**

Q. **It goes on, I believe Mr. Breisblatt asked you about this specific language right here: "In aqueous solutions, they frequently observed notable increase in the drug solubility due to formation of water-soluble," go to the next column, "drug polymer complexes, but sometimes phase separation was observed which was characterized in pharmaceutical systems as rather embarrassing incompatibilities."**

Do you recall Mr. Breisblatt asking you about at least the first part of that sentence?

A. **The first part, yes.**

Q. **But what about the second part? What is the rather embarrassing incompatibilities being discussed?**

A. **You are having a phase separation.**

Q. **What does that mean?**

A. **It can mean precipitation out, salting out, crystallization out.**

Q. **Was that the problem you were worried about all along in your formulation efforts of Alphagan P?**

A. **Yes.**

Q. **Thank you.**

MS. BROOKS: No further questions, Your Honor.

THE COURT: I will give you another round, Mr. Breisblatt. And Ms. Brooks can return for an additional redirect.

MR. BREISBLATT: Thank you, Your Honor.

RECROSS-EXAMINATION

BY MR. BREISBLATT:

Q. **Dr. Olejnik, is PVP and SEC claimed in your invention?**

A. **I would have to go back and look at which invention you are referring to.**

Q. **Your patents right up there, where you describe your various solubility enhancing formulations, isn't PVP one of**

them, sir?
A. I believe that is correct, yes.
Q. Do you have JTX-080 in front of you, that is Mr. Padilla's lab notebook.
A. Yes.
Q. What Mr. Padilla is doing is he is comparing the new formula to Alphagan, isn't he?
A. I would have to go back and look at the actual Alphagan. But I am assuming that -- well, the pH -- which page are we looking at?
Q. We are looking at Page AGN 0066787. So when he says, "The purpose is to formulate a new brimonidine formula using a Refresh Tears base," and under there he has the dots, he is talking about the difference between this formula at least when it comes to CMC, and the Alphagan formula. Correct?
A. I don't know.
Q. Because Alphagan doesn't have CMC, does it?
A. No, it does not.
Q. But Refresh Tears does have CMC, doesn't it?
A. Yes, it does.
Q. And the use of a borate buffer to lower pH, that is a common laboratory technique, isn't it, sir?
A. Primarily, you use phosphate buffers, citrate buffers, borates came into a certain mode at point in time. It has

become more common.
Q. In 1999, it was known that you could use a borate buffer to lower pH. Correct, sir?
A. That's correct.
Q. And when he talks about Purite or chlorite as a more gentle preservative, that is compared to BAK. Right? Because BAK was what was being used in Alphagan. Correct?
A. I assume that was his line of thinking, yes.
Q. So, again, what we are looking at are differences between the Alphagan product then presently on the market and this product that was going to be made using brimonidine tartrate and Refresh Tears. Correct?
A. No.
Q. Well, one more time, sir. The original Alphagan didn't have CMC in it, did it?
A. No, it did not.
Q. And the original Alphagan didn't use Purite, it used BAK, which was known to be a harsher preservative. Am I correct?
A. You are correct.
Q. And you needed the borate buffer because you already had Alphagan at a lower pH than 7.0. Correct?
A. Could you repeat that question, please?
Q. Sure. You needed the borate buffer because the original Alphagan formulation was lower than 7.0. Correct?

A. **You could have used another buffer system for that purpose.**

Q. **Now, was it your decision to use the borate buffer, or was that something Mr. Padilla decided on his own?**

A. **I don't remember what Angel Padilla -- I don't know. I don't recall.**

Q. **And you weren't involved in this lab work, were you?**

A. **I wasn't in the lab, no.**

Q. **So the only two differences you pointed out to us, other than minor variations in the percentage between Refresh Tears and the Alphagan P, or your patented invention, is the use of the borate buffer, which wasn't in Refresh Tears, simply to lower the pH, and that lower pH. Am I correct?**

A. **No. I would say minor variations. In my career in formulation work, minor variations can have a very profound effect.**

Q. **Any other difference in the chemical makeup, sir?**

A. **In terms of the excipients, no.**

Q. **You keep on saying the -- the use of the word "excipients." Refresh Tears has Purite, which you used. Right?**

A. **Used Purite.**

Q. **Has CMC, which you used out of Refresh Tears. Right?**

A. **Not out of Refresh Tears. It is in Refresh Tears.**

Q. **Yes. Thank you.**

So you used CMC as it was in Refresh Tears. Correct?

A. **We used CMC, that's correct.**

Q. **And the only thing you left out from the -- what you added was a borate buffer to change the pH. Am I correct?**

A. **We added in a sodium borate.**

Q. **And that was to affect pH?**

A. **That was as a buffering capacity.**

Q. **And, again, that is to affect pH. Am I right?**

A. **Well, borates have another activity beyond pH.**

Q. **Do they affect pH, sir?**

A. **They do affect pH.**

Q. **Was there anything else you added to the Refresh Tears formula to reduce the pH other than the borate buffer?**

A. **There could have been sodium hydroxide, hydrochloric acid, as you are adjusting the pH itself.**

Q. **My question is: What else did you add to the Refresh Tears formula to adjust the pH besides the borate?**

A. **Boric acid.**

Q. **Anything else?**

A. **Not that I am aware of.**

Q. **Now, let's look at what we have marked as AG -- what is marked as DTX-341. I just want to make sure we are on the same page.**

Are we in agreement, sir, that Table 2 -- and let's go to 219704 -- Column 2 is the use of CMC and CMC only in that aqueous solution at 0.25 percent with whatever the list of drugs is there?

A. **It is. And the way it was prepared is a saturated, supersaturated system.**

Q. **Because --**

A. **It's questionable in terms of the analytical methodology that was used. They weren't validated methods.**

Q. **Wait a minute. This is a refereed journal. You told us that, didn't you?**

A. **It's refereed. But my issue, and I have seen it many, many a time, your professors need to close their ears, they are very good friends of mind, the professor at the University of is Strathclyde, I understand, having gone into industry, the importance of validated analytical methods. You need to understand response factors. You need to understand the degradation of compounds, particularly when they are being heated up to 120 degrees Centigrade. You can change the actual response factor and find that you have a higher value which is incorrect. And these systems are supersaturated systems, in my opinion.**

Q. **Let me see if I understand this. A refereed journal comes out and says, CMC aids in the solubility of drugs, and you, because you are more skilled than one in the art,**

simply wants to ignore it. Am I correct?
A. Could you repeat that again?
Q. Sure. A refereed journal comes out before your invention and tells us that CMC can increase the solubility of aqueous drug formulations but you want to ignore it because you don't believe it. Am I right?
A. I am not ignoring it. I am looking at the methodology and the way these solutions were prepared. Let's understand that. How, when you boil compounds, you create supersaturated systems. It's a known fact.
Q. And this refereed journal tells us, makes a conclusion that one skilled in the art would read, that you can use CMC to make an aqueous drug more soluble. That is the conclusion. Correct?
A. Well, that's a conclusion. That doesn't mean to say that the person or the persons refereeing understood the facts that these were supersaturated systems.
Q. I understand, sir, that you are far more knowledgeable than one skilled in the art and that you are an extremely bright individual. But the paper says what it says. Am I right, sir?
A. Well, I appreciate the previous words. But I have a professional difference of opinion on this paper.
Q. And professionals can differ. Am I correct?
A. Absolutely.

Q. **Sir, am I correct that your ultimate finding was that CMC added to the solubility of brimonidine tartrate?**

A. **Could you repeat that again?**

Q. **Sure. Wasn't your ultimate finding that CMC aided in the solubility of brimonidine tartrate?**

A. **We saw CMC as a solubilizing enhancing component, yes.**

Q. **Same conclusion that the author of this article reached, isn't it, sir?**

A. **No.**

Q. **I am sorry. Didn't the author find, on Page 19707, that, in our study, the addition of a very small amount of PVP, CMC, or HPMC resulted in a significant increase in the aqueous solubility of most of the drugs tested?**

A. **Where are you reading now?**

Q. **AGN 0219707.**

A. **That is a discussion. It is not a conclusion.**

Q. **That's the same conclusion you reached three years later. Right, sir?**

A. **Well, I reached it because we were making systems under room temperature conditions. We were not boiling the system up.**

Q. **Same conclusion, sir. Right?**

A. **The wording --**

Q. **Sir, is it the same conclusion you reached?**

A. **No.**

Q. **All right.**

A. **I have a different position, I am sorry.**

Q. **So you did not find that --**

A. **Well, I did studies, they were well controlled studies with appropriate methodologies.**

Q. **Let me see if I recall correctly. In all of the claims in the four patents in issue, do you mention in every one of those claims where you talk about CMC room temperature?**

A. **It says 21 degrees in there.**

Q. **That is only in one patent, isn't it, sir?**

A. **I would have to go back and look.**

Q. **And that's the one patent where you don't call for CMC. Do you still have your book in front of you? Why don't you look at JTX-2, if you have your small book that your attorney gave you. If we look at what is claimed, sir, beginning on page 0942411 of the '873 patent, do you see any room temperature in any of those claims where CMC or a solubility enhancing component is mentioned?**

A. **This is Claim 1 on Column 7.**

Q. **You start at Claim 1, sir. Do you see anyplace where room temperature is mentioned?**

A. **No, I don't.**

Q. **When you say "room temperature," I want to make sure we are on the same page. What is "room temperature"?**

A. **Room temperature is 21 degrees.**

Q. **Which, for those of us who don't know Celsius, what is it in Farenheit?**

A. **Don't ask me. I would have to do the math.**

Q. **Is it about 72 degrees Farenheit?**

A. **I would have to do the math.**

Q. **Would it be as high as 88 degrees Farenheit?**

A. **No.**

Q. **Sir, would you turn, then, to Column 13, and JTX-03, which is the '210 patent --**

A. **JTX-003?**

Q. **Yes.**

A. **Which column am I looking at?**

Q. **You are looking at 13. And I am looking at Example 1.**

A. **Okay.**

Q. **Do you see the line that begins at 12 that says, "Likewise, the temperature may be varied for, example, solubility curves may be performed at 37 degrees Centigrade"?**

A. **Yes.**

Q. **That's 98.6 degrees Farenheit?**

A. **Physiological temperature, yes.**

Q. **But that's above room temperature, isn't it?**

A. **That's above room temperature, yes.**

Q. **Now, let's look at the claims of this patent real**

quick, and, again, in any of the claims of the '210 patent, beginning at 0226842, do you see any claim involving room temperature?

A. In Claim 1?

Q. In any of the claims, sir. Any mention of room temperature, sir?

A. I haven't seen it so far as I am going through.

Q. I will represent to you that it's not.

A. Okay.

Q. Why don't we look at the '834 patent, beginning with Claim 1. I will represent to you, if you look through that, there is no mention of room temperature.

MS. BROOKS: Excuse me. It is completely misstating the document, Your Honor.

MR. BREISBLATT: I apologize. Counsel is right.

BY MR. BREISBLATT:

Q. If we look at Claim 10 --

A. At about 21 degrees Centigrade.

Q. Does that claim call for any kind of solubility enhancement?

A. It says "a therapeutically effective aqueous ophthalmic composition."

Q. Does it mention anything in Claim 10 or its dependent claims about having a solubility enhancing component?

A. It doesn't say anything about solubility enhancing

component, per se.

Q. **Now let's look at the '337 patent.**

Do you see any mention of room temperature in any of those claims?

A. **No.**

MR. BREISBLATT: I have no further questions, Your Honor.

THE COURT: Mr. Boggs.

BY MR. BOGGS:

Q. **Being a graduate of the University of Kansas, Dr. Stella will be relieved to know that I know the conversion from Celsius to Farenheit?**

Dr. Olejnik, I have a couple followup questions.

Did the '834 patent evolve out of Allergan's effort to reformulate Alphagan?

A. **I suppose so, as it was our project, by the way.**

Q. **And, in fact, one of the objectives of the brimonidine X team was to get patent protection. Right?**

A. **That was a business marketing desire.**

Q. **Now, we spent probably about three-quarters of an hour looking through the patent for various terms. Can you and I agree that the terms glaucoma: And "intraocular pressure" do not exist in the '834 patent?**

A. **I haven't seen those words specifically, "intraocular pressure," no.**

Q. **Nor "glaucoma." Right?**

A. **That's correct.**

Q. **Now I would like to take a look at Claim 1.**

A. **Of the '834?**

Q. **Yes. Now, you spent some time talking about therapeutically effective. I have a couple more questions about that.**

How do you measure therapeutic effectiveness as it's used in this claim?

A. **Well, if you go to Column 3, I think it's Line 36 -- excuse me, Line, I think it's Line 24, The preferred embodiment compositions provided which includes an alpha-2-adrenergic agonist component in an amount effective to provide at least one therapeutic benefit to a patient to whom the composition is administered.**

Q. **First, you have to decide what the therapy is. Is that right?**

A. **Well, yes, that's fair.**

Q. **And then you have to decide what the benefit would be. Is that right?**

A. **Through clinical studies, yes.**

Q. **Through clinical studies?**

A. **Yes, sir.**

Q. **And then you would have to do some experiments. Is that right?**

A. **There is a whole series of studies, experiments, that we would conduct in the course of development, yes.**

Q. **And then you would have to decide whether the benefit had been achieved. Is that right?**

A. **You look at certain end points, criteria that you have established, yes.**

Q. **So you would then have to establish the end points before that. Is that right?**

A. **Not necessarily. It's as you are going through the course of your work, through animal studies, so on and so forth, you are building a profile. Ultimately, you will have certain clinical end points that are defined.**

Q. **What is it that you do that measurement on?**

A. **It depends on the protocol that is established.**

Q. **There could be several of those?**

A. **There could be a number of those, yes.**

Q. **And you would have to know what those were. Is that right?**

A. **There are I think people skilled in the art would know what those are, yes.**

Q. **Now, if you have a bottle of Alphagan P, .15 percent, where does the patent teach you how much to put in the eye to treat glaucoma?**

A. **I would go again back to what I have said here, to observe the composition which includes an alpha-2-adrenergic**

agonist component in an amount effective to provide at least one therapeutic benefit.

Q. **So you run a series of experiments, if you are reading this patent, you want to know how much that is, you have to run some experiments and see what they tell you. Is that correct?**

A. **Well, it's the course of standard practice in pharmaceutical development. You have Phase 2, dose ranging studies.**

Q. **Phase 2 studies, those are where you study the safety and efficacy of the drug?**

A. **Yes. You can do safety in phase one and you actually move into Phase 2 to do dose ranging studies. Sometimes you bracket the concentrations.**

Q. **Those are with human patients. Right?**

A. **They are with human patients.**

Q. **Okay. Let's go back to Claim 1. Now, while you were going through the patent before, Ms. Brooks pointed out several instances where the number 7 was in the patent. Correct?**

A. **That's correct.**

Q. **You never did see 7.0, did you?**

A. **I see 7, and I do recall our deposition in terms of our discussion, debate over 7.**

Q. **7.0 is not in this patent, is it?**

A. **It's 7. 7 is 7.**

Q. **Okay. Look at Table 4, IV. Now, do you recall testifying about this?**

A. **Yes, I do.**

Q. **Now, your discussion about this on redirect started with the preferred pH from the specification of 7.5. Do you remember that?**

A. **Yes.**

Q. **And you looked at this chart and you found something close to 7.5, I guess, 7.56. Is that right?**

A. **It's about 7, yes.**

Q. **And you found this data point, .1451?**

A. **Yes.**

Q. **Is that right?**

A. **That's correct.**

Q. **And as we discussed yesterday, this data from Table 4 was derived from samples containing .2 percent brimonidine. Is that right?**

A. **Well, let's understand what we mean by ".2 percent." When you do those studies, people knowledgeable in the art of solubilization studies, solubility studies, pH solubility studies, would be providing an excess amount of drug. It was just a starting point in terms of the study that was conducted.**

Q. **And this sample that was studied also contained CMC.**

Is that right?

A. **It contained CMC, a variety of concentrations of CMC.**

Q. **In fact, at the top of that column, it says it contains 0.5 percent CMC. Is that right?**

A. **That is correct.**

Q. **Now, Alphagan P does not have a pH of 7.5. Is that right?**

A. **The product in the marketplace does not, no.**

Q. **It has a pH of 7.2. Is that right?**

A. **That's the target pH, although there is a specification, a range of pH.**

Q. **This isn't Alphagan P that we are looking at. Right?**

A. **Well, in that particular case, it wouldn't be the product that's being marketed out there, no.**

Q. **I am not sure I understood your answer. It's not Alphagan P. Right?**

A. **It's not Alphagan P. It's a pH solubility study.**

Q. **I think I had a double negative. I apologize for that.**

A. **All right.**

MR. BOGGS: That's all I have, Your Honor. Thank you.

THE COURT: Ms. Brooks.

MS. BROOKS: Your Honor, just very briefly.

FURTHER REDIRECT EXAMINATION

BY MS. BROOKS:

Q. **I want to ask about the question Mr. Breisblatt was asking regarding room temperature in your tests. He showed you, Dr. Olejnik, first to look at Example 1 of the patent, and let's just work off the '834, since we have been working off that throughout. Of course, I misplaced the page that had the Sample 1.**

Here we go. Example 1. This example, Example 1, is that describing how the studies were done that resulted in the data in Table 2?

A. **Yes.**

Q. **And was Table 2 -- what is Table 2? What does that reflect, that data?**

A. **Again, solubility of brimonidine tartrate over the pH range 5 to 8.**

Q. **So even when the studies are done where it -- the solution is heated up to 98.6 degrees Farenheit, does Table 2 reflect that the solution in the brimonidine still falls off, somewhat precipitously, as the pH goes up?**

A. **Yes.**

Q. **Now let's look at how you did your solubility studies, where -- when I say "your," meaning Allergan's, when you looked at the effect of carboxymethylcellulose when it was combined with the brimonidine. Is that reflected in the figure, which is Figure 1 of the patent, which is on the**

second page, is that reflected in Figure 1?

A. **From these solubility studies, we produced this analysis of variants, and over and throughout it shows the impact of variables. So the answer is yes.**

Q. **A nova graph?**

A. **When you do an assessment of these data points, it is common routine to do a nova analysis.**

Q. **If you can turn to Column 15, and let's go to Table 4. Did the data in Figure 1 come from the data in Table 4?**

A. **From Table 4, yes.**

Q. **And, now, let's look at how those solutions were made. If we could stay with Column 15 and go up to Line 24. "The vials containing the sample solutions were placed on a laboratory rotator and left for" -- can you pronounce that word for me?**

A. **"Equilibration for 15 days at room temperature."**

Q. **At what temperature were these studies done?**

A. **21 degrees C.**

Q. **And what is that?**

A. **Room temperature.**

MS. BROOKS: Thank you.

THE COURT: Is that it?

MS. BROOKS: That is it, Your Honor. Thank you very much.

THE COURT: You are excused, Doctor.

THE WITNESS: Thank you.

MS. BROOKS: Your Honor, I am not sure if Dr. Olejnik wants to, but may he stay in the courtroom?

THE COURT: Any objection?

MR. BREISBLATT: No objection.

MR. BOGGS: No objection, Your Honor.

THE COURT: You may stay, Doctor.

THE WITNESS: Thank you.

(Witness excused.)

THE COURT: Your next witness, Ms. Brooks.

EDWARD DAVID SPENCER KERSLAKE, having been duly sworn as a witness, was examined and testified as follows:

MS. BROOKS: Your Honor, Dr. Kerslake's examination is going to be conducted by Chad Shear.

I am not sure if he has been introduced to the Court yet.

THE COURT: He has not.

MS. BROOKS: Your Honor, this is Mr. Shear from Fish & Richardson.

THE COURT: How do you spell that?

MR. SHEAR: S-H-E-A-R.

THE COURT: Good afternoon, Mr. Shear.

DIRECT EXAMINATION

BY MR. SHEAR:

Q. **Dr. Kerslake, would you describe your educational background for the Court, please?**

A. **I have an undergraduate degree in pharmacy, a Ph.D. in the pharmaceutical sciences. And I have an M.B.A.**

Q. **Could you please describe your work experience?**

A. **After my undergraduate degree, I went to work for a pharmaceutical company in England, Sterling Research, that became part of Aventis.**

And after my Ph.D., I went to work for Allergan in the South of France, spent about three years there, then moved to the Irvine headquarters. I was -- while I was in France, I was head of formulation. And then when I moved to California, I was a scientist, and I was promoted to senior scientist.

I left Allergan in the fall of '98 and joined a strategy consulting firm called The Monitor Group. Spent five years there as a strategy and management consultant working on business cases, until I joined one of my clients, which was a startup, and spent about two years at that startup before joining, eventually joining Boston Scientific, where I am currently the vice president of program and portfolio management.

Q. **Dr. Kerslake, since you left Allergan in 1998, have you worked as a scientist?**

A. **No.**

Q. **Since you left Allergan in 1998, have you done any work as a formulator?**

A. **No.**

Q. **Dr. Kerslake, have you heard of the brimonidine X project?**

A. **I have. It was the name that we had given to the project to improve on the original Alphagan formulation.**

Q. **What was your role in the brimonidine project?**

A. **I was the lead formulator. And I had responsibility for the CMC sub-team, which is chemistry, manufacturer, and controls sub-team.**

Q. **The CMC sub-team, that is not carboxymethylcellulose?**

A. **No, it is different. I think it is a document that you prepare for the FDA. It is a filing. It has to do with chemistry and how you make the product and so forth.**

Q. **Would you please describe for the Court your responsibilities as the lead formulator on the brimonidine X project?**

A. **Sir, I was responsible for coming up with the different options that we had to reformulate for coming up with the different options on the product, the different ways we could improve on it. Then I would work with one of my lab technicians and direct him to go and conduct the experiment for me.**

Q. **How did you approach coming up with the different**

options for the reformulation you just referred to?

A. **For the Alphagan project, we used a wide number of different formulations. Orest and I would brainstorm together about a range of plausible approaches we could use. Then I would go back, work on those formulations and get Angel to do them. We used a lot of formulations in the development of that product.**

Q. **Why did you use a lot of formulations?**

A. **I didn't know which of them, if any, would be successful. Formulating is not easy. And we wanted to try as many as we possibly could to see if there was something interesting coming out of those formulations.**

MR. BREISBLATT: Your Honor, his voice is dropping.

THE COURT: We are going to try to pump the volume and see if that will help a little bit.

BY MR. SHEAR:

Q. **Dr. Kerslake, in the development of the various formulations that you referred to a second ago, I would like to focus on that for a few minutes, have you prepared a demonstrative to assist us today for going through this?**

A. **I did.**

MR. SHEAR: Your Honor, would you mind if he steps down.

THE COURT: As long as he keeps his voice up.

BY MR. SHEAR:

Q. **You have to step up?**

A. **Okay.**

Q. **If you would just step down and place the board on the easel so we can see it.**

(Witness steps down from stand.)

A. **Is it okay if I stand over here?**

Q. **If you really project.**

A. **I will try.**

Q. **Dr. Kerslake, could you explain for us what it is we are looking at?**

A. **Yes. This is a formulation development timeline that I put together. It covers approximately the two-year period from the tail-end of '96, which is when I was given responsibility for the formulation of the Alphagan improvement, through to the end of '98, which is the time that I left working at Allergan.**

It's a pretty complicated chart. What I tried to do is use a different color for each of the formulations that we tried in eventually getting to the final formulation.

I also kind of clustered them according to kind of color schemes. I tried to make it a little simpler. I tried not to put everything on this chart. I had when did we first think about working on these formulations through

to the point at which the work stopped or I didn't work or largely finished. So this bar in between shows us working on the formulations, either me directly or somebody else in the company.

Then these bullets tie into major milestones, so maybe an animal study or the human Phase 2 study so you can see where it is on the timeline.

Q. Dr. Kerslake, if we could focus on the work that was done in the December of 1996 time frame, and if you could explain sort of the formulations in that first time period.

A. Okay. So, when we first started that project, we had about ten or so formulations, mostly gels. There was also an emulsion. And our working hypothesis was that you could get better absorption --

THE COURT: Hold on a second, Doctor.

(Pause.)

THE COURT: Doctor with, while we change out those batteries, you got to keep your voice up, please.

THE WITNESS: Okay.

So I think your question was?

BY MR. SHEAR:

Q. We were discussing the first group of formulations, the work from the December 1996 time frame?

A. So, for this initial batch, there were some gels and there was an emulsion. And our original idea was that by

having a more viscous formulation by using a gel, I think it was a drop of a gel, we would have more residence in the eye and the drug would be better absorbed by the eye.

We also had a hypothesis that by using a tip that delivered a smaller drop into the eye that more of the drug would be kept in the eye and would be available.

So this is some effort that I had ongoing to develop and engineer these new drops.

Some of these products fell out pretty quickly, the carbopol 980, the Allergan new gel, which was too experimental, and the nano systems gel which we found released formaldehyde, which was obviously a reason to discontinue.

THE COURT: Doctor, we are going to interrupt you one more time. Let's see if we can improve the situation.

(Pause as microphone is attached.)

BY MR. SHEAR:

Q. Dr. Kerslake, let's move forward a little bit on the timeline. Look at the work that was done in the February-March 1997 time frame, if you could discuss that?

A. Okay. So I think I mentioned here, this was the first brainstorming. There were three brainstorming, there was this session, a session here, then the final session. This one, we had an idea of using a new product called

perfluorodecalin, which was a chlorofluorocarbon. So think of this as like water but it has twice the density of water. But it's not water. It looked to have some real promise for this formulation.

The downside was, in this kind of time period, chlorofluorocarbons would show the same thing you have in a refrigerator coolant or a spray bottle. I think it was known that they were causing damage to the ozone layer. So many companies were taking these products, this excipient out of their products.

It didn't seem like a smart idea to be introducing a new product that had CFC's. So even though it looked initially promising, we decided that it just didn't make any sense.

Q. **Dr. Kerslake, if I could just interrupt for a moment.**

A moment ago, you referred to these groups as brainstorming sessions?

A. **Yes.**

Q. **Who was involved in the brainstorming sessions?**

A. **Usually Orest and myself.**

Q. **If we could move forward now to the work that was done, at this angle, it is hard to see, sort of the June of '97 time frame, and explain some of those formulations?**

A. **Yes. So there is a couple of formulations here. There was this Gelrite formulation that I believe wasn't**

compatible with the tartrate in the brimonidine. So I think that caused that formulation to fail. The other one that we looked at was these formulations based on the Refresh Purite formulation, we had a brimonidine pure .2 percent and also one with cyclodextrin being prepared.

Q. **Dr. Kerslake, whose idea was it to begin working with the brimonidine-Purite formulation to which you have referenced below?**

A. **It would have been Orest and myself in the sessions.**

Q. **After you and Dr. Olejnik -- the "Orest" you mentioned, that is Dr. Olejnik?**

A. **Yes.**

Q. **After you and Dr. Olejnik had the idea to begin working with brimonidine-Purite as it is labeled there, what did you do next?**

A. **Actually, the first thing that I did after coming up with the initial formulations, or getting Angel to do that work, was to get some solubility studies done because of the results that Angel had given me.**

Q. **If I can just interrupt there for a second?**

Could we have up JTX-80.

THE COURT: Does your IT person have a surname?

MR. SHEAR: Exline, I apologize, Your Honor.

BY MR. SHEAR:

Q. **Do you recognize Page 1 of JTX-80?**

A. **I do.**
Q. **What is this?**
A. **This is the first page of the lab book of Angel Padilla, who was the technician that worked for me.**
Q. **And, I am sorry, who was Angel Padilla?**
A. **Angel was a new technician that had just started work, I think this is his first piece of work, working with me. He was new reporting to me and new to my group. I think Angel was -- I don't think he was a formulator by training. I think he was a biologist. But this was the first experience that I had working with Angel.**
Q. **And, Dr. Kerslake, looking at the work that's on Page 1, could you explain what you asked Angel to do?**
A. **The purpose was to formulate the brimonidine formulation using the Refresh Tears as a base, changing the pH, using the Purite as a more gentle preservative. It is the first attempt at doing these two formulations, at least one of these two formulations that I showed you here.**
Q. **When you asked Mr. Padilla to do this work, perform this experiment, did you think it would work?**
A. **No, I didn't.**
Q. **Why not?**
A. **I expected that the brimonidine-Purite would be insoluble at this pH.**
Q. **Moving forward with this experiment, could you explain**

what the results were?

A. I think Angel found that it didn't precipitate, versus the results that we had seen earlier with brimonidine.

Q. Dr. Kerslake, before I go back to the timeline, if you could --

THE COURT: Doctor, could you look at that device and see if you can turn the volume up a little bit? Is there a volume control on there at all.

THE WITNESS: On, off, and battery check.

BY MR. SHEAR:

Q. Dr. Kerslake, this work, referring to your timeline, could you point out when this work was done?

A. This first formulation would be the first two bullet points that you can see there on the label, you can see on the chart here brimonidine-Purite .2 percent, that is that orange dot there, that's what this experiment corresponds to.

Q. Once you had these results from Mr. Padilla, what did you do next, if anything?

A. I asked Angel to go and do a solubility study with brimonidine in this formulation, because I didn't believe his results.

Q. And on your timeline, where is that work referenced?

A. If you can see those two green diamonds there, I tried to show solubility studies on this one as green diamonds.

So you can see, there is that first solubility study directly after this initial trap, as I call it. Then I actually asked him to repeat it. You can see, there is probably a three- or four-month period in December to February, it was page after page in his lab book of solubility studies.

Then I asked George Ambrus to work with Angel, because I was a little skeptical of Angel's results, and George then spent another few months repeating that study, which is what you can see in the long grade.

THE COURT: Let me interrupt. This is the unusual situation where the fact-finder gets to talk with the lawyer. That chart, with respect, is not helpful for me. It is too busy.

MR. SHEAR: That is understood. No problem, Your Honor.

BY MR. SHEAR:

Q. **Dr. Kerslake, you mentioned a moment ago that you had asked Mr. Ambrus to assist Mr. Padilla in performing a solubility study.**

Did Mr. Ambrus do that?

A. **He did.**

Q. **What was the result of that study?**

A. **Mr. Ambrus' results corroborated the earlier findings of Angel. He found that brimonidine tartrate was soluble**

and the CMC was aiding the solubility.

Q. **Why did you ask Mr. Ambrus to assist, as opposed to someone else?**

A. **I had, I think I mentioned, this was the first time I had a chance to work with Angel. Over this six-month period, I became a little skeptical of Angel's ability, in part because I was getting these results that I didn't believe.**

And Mr. Ambrus was in the pre-formulation group. These types of solubility studies are what one would typically do in the pre-formulation group, and Mr. Ambrus was also a very, very good scientist. And I needed a result that I could trust.

Mr. Ambrus conducted the study and had the result, and I believed him.

Q. **Dr. Kerslake, if we could look at Figure 1 of JTX-3, it's in the binder in front of you. It's also on the screen in front of you.**

Does this figure look familiar to you, sir?

A. **It does.**

Q. **And what does it show you?**

A. **This is the result of the work that I had asked Mr. Ambrus to do. That shows the solubility of brimonidine at different concentrations of CMC. It shows CMC increasing the solubility of brimonidine.**

Q. **Dr. Kerslake, in your experience at Allergan, would you formulate an ophthalmic product on the edge of solubility?**

A. **At the solubility limit, no, I would not.**

Q. **Why not?**

A. **I can't control how one of our patients would use one of our products. It's not laboratory where they may be, in the worse case, they may be putting it in their glove box in their car when it is 120 degrees. You are going to lose water through the plastic vial and the concentration of the drug in that product is going to go up. That would cause a problem.**

Plus, there is some flexibility in the formulation, itself. There are tolerances for each of the many, many ingredients. And each of those could have an impact on the solubility.

So I would want to know what worse case in that formulation my drug was not going to be insoluble. I couldn't do that by picking it right there.

Q. **Thank you, Dr. Kerslake.**

THE COURT: All right. Let's a short stretch before we begin cross-examination.

(Recess taken.)

THE COURT: Please take your seats.

MR. BENSON: Good afternoon, Your Honor.

Your Honor, may I have leave to approach Ms. Walker and the witness to provide documents.

THE COURT: You certainly do, counsel.

MR. BENSON: Thank you.

CROSS-EXAMINATION

BY MR. BENSON:

Q. **Good afternoon, Dr. Kerslake. Nice to see you again. I would like to put up Claim 1 of the '834 patent, just very briefly.**

Dr. Kerslake, during direct examination, you indicated that one of the goals of your invention was to make sure that brimonidine tartrate was soluble over a wide range of temperatures, and I think you referred to that as robustness. I think you said you wanted to make sure, in the worst case scenario, that the drug didn't become insoluble.

What is the temperature requirement of Claim 1 of the '834 patent?

A. **I didn't say that the temperature dependence was the only element of robustness. It is one of the variables that might have an impact on the formulations.**

Q. **Dr. Kerslake, you specifically referred to 120 degrees Celsius. What is the limitation on this patent as it relates to temperature?**

A. **It says 21 degrees, there.**

Q. **About 21 degrees, actually. Correct?**

A. **It does?**

Q. **Is 120 degrees about 21 degrees?**

A. **No.**

Q. **So this doesn't really relate to robustness at all, does it?**

A. **The patent?**

Q. **Well, I mean, certainly there is no requirement that the compound remain soluble over a wide range of temperatures, does it?**

A. **What it says, something to the effective aqueous ophthalmic composition.**

Q. **We have been talking a lot about solubility enhancing components today, haven't we?**

A. **Me personally?**

Q. **Collectively we, if I might --**

THE COURT: He has been sequestered.

BY MR. BENSON:

Q. **Dr. Kerslake, is Allergan a public institution? Do you know what I mean by that? In other words, is it publicly traded, stocks?**

A. **It is publicly traded.**

Q. **So it is in the business of making money, isn't it?**

A. **I would believe so, for the shareholders.**

Q. **Okay. Now, in 1997, was brimonidine a big product for**

Allergan?

A. **The Alphagan product, I think it was a decent product. To be honest, I am not sure exactly.**

Q. **In the $100 million a year range?**

A. **To be honest, I was a scientist at the time.**

Q. **You have no idea whether it was a big product, a small product, anything of that nature?**

A. **I can't recall at this time whether it was a large product or a small product for Allergan. Again, it wasn't something that I paid attention to at the time.**

Q. **But you are aware that Alphagan was favoring generic competition. Correct?**

A. **I have seen that from the documents, yes.**

Q. **And that there was a fast track redevelopment of the brimonidine tartrate compound in view of the imminent generic entry, competition entry. Correct?**

A. **I am not sure if it was in view of the generic entry. I know that in any development effort, we tried to get the product developed as quickly as possible. Whether or not it was just the generic entry in this case, I can't remember.**

Q. **Okay. And one of the other requirements was that you wanted patent protection for the new reformulation. Isn't that correct?**

A. **As you said, it was a publicly traded company. They were in the business of at least being able to justify the**

investment that they would make in R&D efforts. So I don't recall being told that it must be a patented product. But I am sure it would have been an advantage to the company to have something that the patent protected.

Q. **So you are a publicly traded institution. You are in the business of making money. You have a drug that, presumably, is pretty successful, or at least somewhat successful because you are worried about generic competition. And you have a fast track for development. One of your considerations is patentability.**

Let me ask you, in that context: Would you try just one formulation?

A. **Absent that context, I would try more than one formulation.**

Q. **So, even without all of those figures, you would still try more than one thing?**

A. **Formulation is very, very hard. You need to try many formulations in order to determine one that might eventually be useful.**

Q. **Absolutely. In fact, that's what's shown on the chart that you have to your left. Correct?**

A. **It is shown, yes.**

Q. **You actually chose a bunch of different formulations right off the bat?**

A. **I think we initially came up with ten potential**

opportunities, and then we added -- again, this is probably not an exhaustive list. It is what I was able to develop over the last couple of days.

Q. **And you are not representing to this Court that brimonidine-Refresh Tears was the only one that worked. Correct?**

A. **There were other formulations that were -- that showed promise along the way.**

Q. **Thank you.**

Now, if we are looking at that chart -- and I am not going to belabor the point because I do think it is a little difficult to look at, but there is one thing that is kind of striking about it. You can almost see it best if you look at it a little blurry. What you realize is that, at the top right, after around June, July of 1997, there isn't a lot going on. But underneath, with respect to the brimonidine Refresh Tears product, there is a couple things going on. Correct?

A. **Yes. I know that some of the earlier formulations, the carbopol, I think by mid-'97, we had some of the results from some of the animal studies we conducted earlier. Those formulations didn't work. I tried to show with these green arrows that, again, there were some formulations we were continuing to work on. But the Refresh formulations now looked really interesting.**

Q. **We established earlier that Refresh Tears went on the market in June of 1997. Are you aware of that?**

A. **I am sorry.**

Q. **I will represent to you now that evidence has been admitted in court today that demonstrates that Refresh Tears came on the market in June of 1997. I will further represent to you that interoffice memorandums have been produced showing that, at that time, the idea to formulate brimonidine with Refresh Tears was proposed, and that it immediately went into development.**

Now, development stops right around June-July 1997, according to your graph, with all -- almost all compositions except for brimonidine Refresh Tears. Isn't that correct?

A. **No --**

Q. **I am just looking at the exhibit that you have entered today.**

A. **Actually, if you look at the data, some of these finish in June. There is a number of them that fall out for different reasons, where we found that the, I think one of them, gel med, we didn't have enough -- there was no toxicity data provided by the manufacturer so we couldn't use that product. There were a number of different reasons why the products didn't work at the time.**

Q. **So you indicated that, with gel med, you had no**

toxicity information available so you couldn't work with that product?

A. **I believe that was the issue with that particular formulation, that the excipient, the supplier of the excipient didn't have the necessary information, the toxicity data. So it would have made it difficult to work with.**

Q. **Okay. What that, in fact, means is it would have taken more time. Correct?**

A. **Or the company might not have been prepared to do the work. To be honest, I couldn't recall --**

Q. **I apologize.**

A. **-- I couldn't recall, again, the records I was reviewing yesterday and the day before as I was putting this together, I saw the reference that said that the supply didn't have the necessary data. But I couldn't remember whether or not we had done anything after that.**

Q. **So you didn't create this chart out of memory? You sat down in the last couple of days and put together this chart based on documents that were provided to you?**

A. **I went through hundreds of documents to try to find dates and the formulations to remind myself. My memory is not good enough to be able to generate that stuff.**

Q. **In the last couple of days, you did that. Correct?**

A. **Right.**

Q. **So, did you do an independent search for documents that might evidence product development?**

A. **Over the past two days or so? I just went through, we had documents of the meeting minutes, I went through them. Angel Padilla's notebooks, I went through. I went through as many as I could, specific dates of when we said we were going to start a formulation, when we had bad news, that the animal results were poor. I tried to make it as simple as possible. But was not too successful.**

THE COURT: It's all right.

BY MR. BENSON:

Q. **Now, you will see at the bottom, there are a couple of things. One of the things that I see was being developed as a brimonidine-Purite was cyclodextrin. Correct?**

A. **That's correct. I started that one, I think, in parallel with the brimonidine-Purite formulation.**

Q. **And you got a patent covering that, didn't you?**

A. **I believe so. To be honest, I haven't paid much attention to the patent since I left. It's been ten years since I left Allergan.**

Q. **Do you usually obtain patents on things that don't work?**

A. **I have no idea, to be honest.**

Q. **Now, we were looking earlier today at what I believe was JTX-008. That was Angel Padilla ---sorry, maybe it was**

088 -- 080?

We looked here at the formulation, which is, I apologize, I will have to find the Bates number. I believe it's AGN 0066787.

That was dated, as we established earlier, June 25th, 1997. We also established earlier that this formulation did not differ in any way, with the one exception of possible change -- or toying with the pH and the addition of brimonidine tartrate. But absent that, it is exactly the same.

A. **Which -- I don't think --**

THE COURT: I am curious, counsel. You seem to have a pattern of engaging in, almost testimony. I understand, you are setting a question up. Was that necessary to ask the question?

MR. BENSON: I think it is, Your Honor.

THE COURT: If it is not, I want you to discontinue the practice.

MR. BENSON: I think it is necessary, Your Honor.

THE COURT: That is fine.

BY MR. BENSON:

Q. **Could I have the next page, please?**

Do you see here, July 18, 1997, again, we were showing here that the results showed that there was no

precipitation at the higher pH range?

A. Yes. That was the surprising result that I was alluding to earlier.

Q. So that was the result that you didn't believe?

A. That was the first time that we saw that brimonidine proved to be soluble. I didn't believe it with Angel's first result.

Q. Whether you believed it or not, the combination of Refresh Tears and brimonidine resulted in solubilization, or at least, according to this document, solubilization of brimonidine tartrate. Correct?

A. I don't think he actually says what it was. I don't think he knew at the time. He just says, There is no precipitation at the higher pH range.

Q. So when it says, no precipitation at a higher pH range, 7.5, that isn't a conclusion about whether or not brimonidine was soluble in that formulation?

A. You specifically said "solubilization." I see no statement in this page about solubilization. So I don't know how you deduce that that is what he thought it was at the time.

Q. Okay. Coming back to the chart for a moment, these previous formulation developments, were those publicly -- was that publicly available information; in other words, Allergan's success with respect to trying to formulate any

of those formulations?
A. What do you mean?
Q. For example, if we look at the top, we see the carbopol formulations?
A. Yes.
Q. Did you publish on that at the time?
A. I don't believe so.
Q. With respect to any of those other formulations, were there any publications demonstrating to the public that Allergan was trying to reformulate brimonidine in that way?
A. I didn't publish, that I recall, on any of this. Whether somebody else did without my knowledge, I don't know. At least I can't remember.
Q. A person of ordinary skill in the art was aware of Refresh Tears as of June 1997?
I will represent.
I will move on.
Now, Dr. Kerslake, you chose Refresh Tears, in part, to eliminate the preservative benzalkonium chloride. Correct?
A. I am trying to recall. There were a number of things that were interesting about the formulation. The preservative, Purite, I am sure, would have been one of them at the time. Again, this is 12 years ago.
Q. And you chose Refresh Tears because you knew it was

soothing and comfortable and tolerant when administered to patients. Correct?

A. **I think I recall it being so. So that would make sense as a contributing factor in choosing elements of that formulation to consider.**

Q. **So it makes sense, considering the Refresh Tears didn't have Purite and it was soothing and comfortable and tolerant, it made sense to choose that as a possible vehicle for brimonidine tartrate. Correct?**

A. **I am not sure what you mean by "made sense." But I am sure if there was -- there were interesting properties around that formulation, I would have considered it, along with many of the other options that we considered here. We tried a lot of things.**

Q. **I would like to talk a few moments, if I might, about the patents that are in suit and which you have been named a co-inventor on.**

As a segue into that, I would like to have Pages 30 and 31 from yesterday's hearing, transcripts Lines 20 to 25 on 30 and 1 to 4 on 31.

Now, the '210 patent, do you understand that to be one of the patents at issue in this case?

A. **I do.**

Q. **It says here that it's been said that this deals with the composition containing alpha-2-adrenergic agonist**

components, and, essentially, the '210 patent talks about not just alpha-2-adrenergic but specifically brimonidine and the use of a polyanion solubility enhancing component, something that had not been done before.

Did I read that correctly?

A. **That's what it does say.**

Q. **Could I please have, again, Page 31 of yesterday's hearing transcript, Lines 5 to 25. Now, this is talking about the '873 patent.**

Do you understand that this is also one of the patents that is being asserted against Apotex in this litigation?

A. **I didn't know specifically, to be honest. I haven't been spending a lot of time looking at the patents.**

Q. **Do you have any reason to doubt that fact?**

A. **I have no reason to doubt nor believe it. If you say that's so...**

Q. **Okay. So, it says here that the '873 patent is described as being an alpha-2-adrenergic agonist, it says it's broader than brimonidine, a solubility enhancing component, is excluding cyclodextrin because, of course, that was a prior art, and an oxychloro component. It says, So, indeed, once again, there was an additional discovery, and that is covered by the '873 patent.**

Okay. Now, I would like to put up JTX-003.

THE COURT: Counsel, let me see you at sidebar.

(The following took place at sidebar.)

THE COURT: What was the purpose of -- what were you trying to accomplish with that? That's prior testimony. Were you attempting to impeach him in some way?

MR. BENSON: No. I am trying to establish whether or not --

THE COURT: Ask him a question, counsel. Don't use prior testimony. That is an entirely improper use of that testimony. And you should be objecting, okay?

MR. SHEAR: Yes, Your Honor.

(End of sidebar conference.)

MR. BENSON: Might I have a moment?

THE COURT: Yes.

(Pause.)

BY MR. BENSON:

Q. **Dr. Kerslake, I am going to provide you with what has been marked as Joint Trial Exhibit 44?**

Dr. Kerslake, this is an interoffice memorandum relating to the brimonidine team, or the brimonidine-X team. Do you recall the brimonidine-X team being the team working on reformulating the Alphagan product?

A. **I do.**

Q. **And this seems to indicate that this is the meeting minutes from a July 30th, 1997, meeting?**

A. **I see that.**

Q. **I would like to take you to the second page. It says here, under III, do you see where it says, In-Site Vision, quote, Aquasite?**

A. **I see that.**

Q. **Is Aquasite one of the formulations identified on your chart?**

A. **Yes, it is. It is the one with the blue line on there.**

Q. **So as of June 30th -- I am sorry, July 30th, 1997, it states here that Allergan was putting on hold any negotiations with In-Site until other options have been thoroughly evaluated. Correct?**

A. **I see that.**

Q. **Now, if we look -- if we go to the previous page, underneath the recommendations, do you see where it says, "Develop a brimonidine/Purite formulation which equals Refresh Tears plus 0.2 percent brimonidine." Correct?**

A. **That's what it says.**

Q. **Now, turning the page back, could we go to Roman Numeral No. 4. It says here, gel-med.**

Now, was gel-med one of the formulations identified on your chart?

A. **It is.**

Q. **Was that the gel-med that we were talking about**

previously?

A. **It was.**

Q. **And it says here the gel-med vehicle solubilizes compounds well. However, due to the short window of opportunity for brimonidine X, this vehicle would not be feasible for fast development for line extension and there is no chronic toxicology data available. Is that correct?**

A. **That's what it says.**

Q. **Is there any indication here that gel-med would not work?**

A. **No. In fact, it says the gel-med formulation should be developed in parallel. It suggests we actually carried on working on it.**

Q. **Okay. Dr. Kerslake, I am now going to bring you JTX-077.**

Dr. Kerslake, one of the formulations Allergan was looking at was a perfluorodecalin formulation. Correct?

A. **That is correct.**

Q. **I would like you to turn to the second page of this document. Do you see at the very bottom it says, PFD Issue.**

Is PFD a common abbreviation used by Allergan for perfluorodecalin?

A. **It is.**

Q. **It says here that perfluorodecalin was dropped because the project was discontinued, not due to any product**

inadequacy. Because our timeline on this project, however, is limited, marketing does not recommend proceeding with this option.

Is it uncommon for the marketing department to make formulation decisions with respect to drugs that are being developed for sale?

A. **I am not sure if this was a formulation decision. This may have been a CFC issue that I was talking about. I found a lot of documents that talked about the CFC issue. So it may have been that one.**

Q. **It says here it was not discontinued due to any product inadequacy. Correct?**

A. **I think I mentioned earlier --**

Q. **I am sorry, if you could just limit your responses to my question.**

It says here it was dropped not due to any product inadequacy. Correct?

A. **That's what it says, yes, there.**

MR. BENSON: Your Honor, I don't have any other questions.

THE COURT: Thank you, counsel. Mr. Boggs.

BY MR. BOGGS:

Q. **Good afternoon, Dr. Kerslake.**

A. **Good afternoon, Mr. Boggs.**

Q. **I believe that you testified that you would never**

formulate at the edge. Is that correct?

A. I believe I said I wouldn't formulate at the limit of solubility.

Q. Okay. Can we have the '834 patent, Table IV.

Dr. Kerslake, do you recognize this table from the '834 patent?

A. I recognize it as one of the tables in the patents. I am not sure specifically which one. If you say it's the '834...

Q. Could you take a look at the '834 patent. I believe it's JTX-4.

A. Okay, I see Table IV.

Q. I would like you to look at the column that is 0.5 percent carboxymethylcellulose.

Do you see that column, CMC?

A. I see that column.

Q. Okay. And on the pH column, I would like you to look down at pH 7.56. What is the value that you see there?

A. 0.1451.

Q. That would be the edge of solubility. Correct?

A. I don't know, to be honest, Mr. Boggs. I haven't looked at these patents in a long time.

Q. Let's look at Figure 1 of the patent. Figure 1 was generated for Table IV. Is that correct?

A. I honestly don't recall. It's been ten years since I

left Allergan.

Q. **What does this figure tell us?**

A. **This figure looks at the, shows the solubility of brimonidine tartrate at different concentrations of CMC.**

Q. **You testified about this when Mr. Shear was asking you about it. Right?**

A. **Yes. I said it was the work that George Ambrus did, Mr. Ambrus.**

Q. **What are those lines on the chart?**

A. **Different concentrations of carboxymethylcellulose and the solubility of brimonidine tartrate at different pH's.**

Q. **Those lines show you the edge of solubility. Correct?**

A. **For this formulation for this particular experiment.**

Q. **That's right. Okay. Now, if you look at 7.5 and you correlate that with the line for .5 percent CMC, what value do you get?**

A. **That's the diamonds, about 1,500 parts per million.**

Q. **Now, go back to Table 4, if you would. Before you do that, please, so it is at that point that that's the edge of solubility. Right? According to this chart?**

A. **According to this chart for this formulation, yes, I think so.**

Q. **Okay. Now, Table 4. Okay. Again, let's look at the crossroads between pH 7.56 and .5 percent CMC., 1451.**

A. **I see that.**

Q. **You would never formulate at the edge of solubility. Right?**

A. **If I was going to sell a product, I would want it to be safe in all of the conditions that a patient might use it in. So I would not formulate it right up to solubility with this formulation.**

Q. **Now, I want to talk about your timeline a little bit.**

A. **Okay.**

Q. **You ended your employment with Allergan in September of 1998. Is that right?**

A. **In the fall of '98, September-October. I can't recall exactly.**

Q. **And at one point in time, one of your lead formulations was a .2 percent brimonidine formulation. Correct?**

A. **We had many lead formulations. It's been like a raise, it's whoever is in front at the time. Maybe -- I can't remember who was first. If you have got a document that says it was a lead formulation, I can't dispute it.**

Q. **Let's take a look at JTX-078. Do you recognize this document?**

A. **What's the number?**

Q. **It's JTX-078.**

A. **It's on the screen. I can see it on the screen.**

Q. **Do you recognize this document?**

A. **Yes. I see my name on it.**

Q. **And if you turn a few pages in, do you see the designation "9115X"?**

A. **I do. I see that.**

Q. **That's brimonidine X lead formulation. Right?**

A. **It is, at the time, yes.**

Q. **And can we find that on your timeline chart?**

A. **I am trying to remember at this point.**

This may have been one of those initial formulations that we tried, maybe the first one that I tried with Angel. I can't be sure, again, Mr. Boggs.

Q. **Did you leave some of your formulations off this chart?**

A. **Probably. As I said, the lead formulation may have been one at the front of the pack. There may have been others at the time. I don't think lead formulation means that that's it, we are ready to go home. It probably means the one that is most probable at this time.**

Q. **Let's look at the lead formulation up here. That's 9115X. Now, that particular lead formulation contained .005 percent Purite. Is that right?**

A. **I see that.**

Q. **And the Purite was a preservative. Is that right?**

A. **I think one of its actions was a preservative.**

Q. **And 9115X contained .5 percent sodium**

carboxymethylcellulose as a viscosity agent. Correct?
A. I see .5 percent CMC there. But it had actions over and above viscosity.
Q. Okay. What is the significance of the low viscosity next to that CMC?
A. I think -- I know we did a lot of work on the manufacturing method. I think it was quite difficult to filter this CMC. So I think there was a high and a low variant. I think the low variant was easier to filter. I think that's what we specify in there.
Q. So a low viscosity CMC was important for the manufacture of the formulation?
A. I believe so at this time.
Q. Do you recall if you included that information in your patent application?
A. I can't recall. I have seen -- I saw the work in Angel's lab book over the last few days as I was going back, and that reminded me because I saw all of the manufacturing filtration work he had there on the different CMC's. So that's what reminded me of that.
Q. Now, 9115X contained .2 percent boric acid. That is a buffer. Right?
A. I think that's the buffer component, part of it. I think that's the buffer component.
Q. And 9115X contained .14 percent sodium borate. And

that's the other part of the buffer. Right?

A. **It says sodium borate decahydrate, yes.**

Q. **And 9115X contained .58 percent sodium chloride. Is that right?**

A. **That's what it says, yes.**

Q. **And we would call that a tonicity agent. Do you recall that?**

A. **I think, yes.**

Q. **And 9115X contained .14 percent potassium chloride?**

A. **I see that.**

Q. **Then people would call that an electrolyte. Is that right?**

A. **I believe in this formulation, those next couple were the electrolytes within the formulation.**

Q. **The calcium chloride, which is the CACL2-2H20, is an electrolyte?**

A. **I see that.**

Q. **And the same with the magnesium chloride on the next line. Is that right?**

A. **I see that.**

Q. **Now, 9115X had a pH of 7.4. Is that right?**

A. **I see that.**

Q. **Does that seem high, a little high to you?**

A. **It's the pH of the ion. So that's a physiological pH.**

Q. **Now, I want you to turn to JTX-9.**

Before we do that, can you go back to 9115X.

Okay. I am sorry to get you off track there. At one point in time, 9115X was the lead formulation, and it contained .2 percent brimonidine. Right?

A. **I see that, yes.**

Q. **And then, at some point later in time, Allergan shifted away from that formulation and went into what is -- or went to what is now Alphagan P, which is a .15 percent. Is that right?**

A. **Yes, I think we went from .2 to .1 to .15.**

Q. **.2, .1, .15?**

A. **I believe, yes.**

Q. **Now, do you recall that they modified the formulation by reducing the concentration, and they did alter the buffer somewhat. Do you recall that?**

A. **I recall that we did pull back the pH a little bit. I think it was a solubility concern at the time, it was very close to the solubility limit. It gave it a little more -- it made the formulation a little more robust.**

Q. **They went from 7.4 to 7.3. Is that right? Or 7.2?**

A. **7.2-7.3, yes. I can't recall now.**

Q. **As I recall from our deposition, you can't recall whether you were involved in that switch. Is that right?**

A. **Well, as I went back over the past couple of days, I did see the .1 percent work did happen while I was there.**

Q. **So, today, you believe you were involved in that change. Is that right?**

A. **Well, it happened while I was at Allergan. So it would have been something that I would have been involved in.**

Q. **So that change took place before you left, before the fall of 1998. Is that right?**

A. **I believe so, yes.**

Q. **You keep looking to the timeline over there. Are you equating the switch to the .15 to something on this chart?**

A. **I see the .15 towards the tail-end of this chart. It would have happened before I left. If I can, my memory is not great, doing this chart in general, this chart was helpful to me.**

Q. **So, it is this last line on the chart at the bottom and the last formulation to begin. Is that right?**

A. **Sorry. Say that again?**

Q. **Is it possible to put this up, JDX-15. Can you see that?**

A. **Yes.**

Q. **So the .15 formulation --**

MR. BOGGS: Your Honor, can I point?

THE COURT: Sure.

MR. BOGGS: Thank you.

BY MR. BOGGS:

Q. **This is the .15 formulation here?**

A. **That is a .15. I am not sure if it's the final one. But it is a .15 formulation.**

Q. **And that happened in the summer of 1998?**

A. **Yes, it looks like May '98.**

Q. **Over here, we have the .1 percent?**

A. **I see that, too. Yes.**

Q. **Back here, we have .2 percent?**

A. **That's correct.**

Q. **Now, you are not sure whether this is 9115X. Is that right?**

A. **I believe it is. We can look at Angel's lab book, and if the two formulations prove to be identical, you could say that.**

Q. **Thank you. I just wanted to nail down some of those facts.**

Now we can go to the patent. In particular, AGN 022620.

Okay. This is also in your notebook. It should be a two-page document, JTX-9.

A. **I don't see anything in this one. 009, you said?**

Q. **Yes. It may be in the other binder. It's probably flagged.**

A. **Okay.**

Q. **My 009 doesn't seem to have the same, unless --**

A. **Is it a page number?**

MR. BOGGS: Your Honor, may I help?

THE COURT: Yes, you may.

THE WITNESS: I can see it, that's right.

BY MR. BOGGS:

Q. **Yes, there you go.**

Dr. Kerslake, would you agree that this is a declaration for a patent application that you filed?

A. **I believe that's what it is, yes.**

Q. **Do you recognize it as the declaration for the '834 patent?**

A. **Does it say that somewhere on this?**

Q. **Well, it's part of a larger file history that you have there?**

A. **Then I don't know.**

Q. **Fair enough. Is that your signature on this?**

A. **That is my signature.**

Q. **Okay. And you dated that in July of 2001. Right?**

A. **I see that.**

Q. **My question is that, it seems that the brimonidine-Purite -- you left Allergan in September of 1998. Is that right?**

A. **That's right.**

Q. **And then almost three years later, you filed a patent application. Is that right?**

A. **If this is the patent application, then, yes, that's my signature.**

Q. **Do you recall a point in time when you were surprised by the fact that Allergan called you to file a patent application, three years after you left?**

A. **I don't recall being -- I am not aware that I was surprised or not when they called me, what is this, eight years ago.**

Q. **Do you recall any of those events at all?**

A. **Being called by Allergan? I remember --**

Q. **Do you recall going through the exercise of signing this declaration for this patent application three years after you had left Allergan?**

A. **This specific document? I remember getting many, many FedEx documents and talking a great deal with Allergan while I was going through this. The specific day on which I signed this, on signing this document as different from other documents, I can't remember.**

Q. **Now, at this point in time, you weren't thinking about science anymore. Right?**

A. **No.**

Q. **In fact, you haven't thought about science for ten years. Right?**

A. **Yes.**

Q. **Ten-plus. Right?**

A. **Yes.**

Q. **In this declaration, you stated that you reviewed and understood the contents of the specification. Correct?**

A. **Yes, it says that.**

Q. **In fact, you signed the declaration, and, so, you believed that at the time. Right?**

A. **I did believe it at the time.**

Q. **And it also says that you read and understood the contents of the claims. Right?**

A. **Including the claims, it says that, yes.**

Q. **So when you filed your patent application in 2001, you understood what the claims meant. Correct?**

A. **I would have -- if I signed it, I read and understood, then I would have read and understood at the time.**

Q. **And we can be fairly confident that the patent application reflected your understanding of things and your full knowledge of things at the time that you signed this declaration. Right?**

A. **If I read -- if I signed it to say that I read and understood it, then I would have been sure to have read and understood the document before signing it.**

Q. **Okay. Let's look at Table 3.**

This is Table 3 from the patent. Do you see that?

A. **I see it.**

Q. **And let's look at Sample 4 in particular.**

A. **Okay.**

Q. **Do you remember talking about this sample during your deposition?**

A. **My deposition with you?**

Q. **Yes.**

A. **To be honest, I don't remember the specific conversation.**

Q. **Why don't you look at the ingredients for Sample 4, if you would?**

A. **Okay.**

Q. **Now, will you agree with me that Sample 4 corresponds, with the exception of pH, which is unstated here in this table, with 9115X? Is that right?**

A. **I don't know. I can't remember the 9115X. If you tell me that these two...**

Q. **It's in your binder, JTX-078.**

A. **Many of the concentrations seem to be similar.**

Q. **Are they exactly the same?**

A. **The ones I have checked so far, yes, with the exception, as you said, of pH and water.**

Q. **Okay. Now, isn't it true, Dr. Kerslake, that when you filed your patent application, you thought that you were filing a patent application on .2 percent brimonidine, 9115X. Correct?**

A. **I can't tell you what I was thinking that my patents might have been in this 2001. Is that what you are asking me?**

Q. **You can't tell me today or you never knew?**

A. **The patents -- I knew at the time that we had done some interesting experiments with the brimonidine formulation, we had found some interesting things and it resulted in patents. But which particular aspects went to which patents, I don't know today.**

Q. **Let's put up Claim 1 of the patent, please.**

Now, this claim has a range of up to .15 percent. Do you see that?

A. **I see that.**

Q. **And 9115X has a pH of .2 percent. Right?**

A. **A pH?**

Q. **Excuse me. Concentration of brimonidine?**

A. **It does. I believe you showed me that.**

Q. **Okay. And, in fact, all the examples that we looked at, Samples 1, 2, 3, 4, and 5, they all contained .2 percent. Correct?**

A. **If you say that's so.**

Q. **Now, your stated objective in reformulating original Alphagan was to improve safety and efficacy. Is that right?**

A. **Yes, and make it a better product.**

Q. **Better product than original Alphagan. Correct?**

A. **I believe that was the objective of the project. Again, it's been ten years. I know there were issues with the Alphagan product and I was asked to see if I could make it better.**

Q. **Now, do you know today whether that had been accomplished by the time you left Allergan in 1998?**

A. **It depends how you mean "accomplished"? We had animal data that showed it was going to be promising, and I had lab data, results from the lab that showed my formulation was good.**

Q. **Is it true that animal data doesn't always translate into human studies?**

A. **I can't do it every time that we do it. But it's a very good indicator.**

Q. **I would like to pull up the transcript from his deposition.**

Do you have your deposition in front of you there, Doctor?

A. **I don't know.**

Q. **It should be the very first thing in the first notebook.**

A. **Yes, I see it.**

Q. **You recall that I took your deposition. Right?**

A. **I do.**

Q. **And you were under oath during your deposition. Is**

that right?
A. I was, yes.
Q. I would like you to confirm for me, through the use of this transcript, that I asked you the following question and you gave me the following answer:
"Question: Okay."
A. Could you point me to the specific page?
Q. 246, Line 2:
"Question: Okay. And one of the objectives of that team was to reformulate the approved Alphagan product. Correct?
"Answer: Improve the safety and efficacy of the marketed product.
"Question: Okay. At the time you left Allergan, had you accomplished that?
"Answer: I can't recall if I had sufficient data in hand to say that the safety was improved. To get the definitive data would have required the Phase 3 data, and that hadn't arrived by the time I left the company."
A. That's right.
Q. Did I ask you that question and did you give me that answer?
A. I see that, yes.
Q. So, with regard to the .15 percent formulation, your complete and operable invention as it would be applied in

practice was not finished when you left?
A. I have no idea what that means.
Q. Was your complete invention finished as it would be applied in practice?
A. I don't know what the definition of that would mean. So I have no idea whether it's yes or no.
Q. Well, what did you contemplate the use of your formulation to be?
A. We were developing a product for the treatment of glaucoma, so, if that's what you mean.
Q. So, was your invention complete for the treatment of glaucoma by the time you left Allergan?
A. I don't know what you mean by that. My invention was completely finished, the formulation work, if that's what you mean. So the formulation was complete.
Q. Phase 3 testing was not complete. Correct?
A. No, I stated that in my deposition, sir.
Q. So did you know if it was operable by the time you left Allergan?
A. What does "operable" mean?
Q. Did it work for its intended purpose?
A. Yeah. We had good results from the animal data. So we believed that it was going to work.
Q. Why did you do Phase 3 studies?
A. To confirm, to prove it to the FDA, to allow the

product to be marketed, they required that to happen. You are not allowed to market a product without a Phase 3 study.

Q. **Were you confident that it would work?**

A. **I don't think they would have started the Phase 3 study given the millions of dollars that it was going to cost unless they were pretty confident that it would be successful.**

Q. **That's right. Phase 3 studies cost millions of dollars. Right?**

A. **I would expect so.**

Q. **How many millions of dollars do Phase 2 studies cost?**

A. **I have no idea. I would guess half that amount, maybe.**

Q. **Things have to be pretty predictable before you go into Phase 2 and Phase 3 studies. Correct?**

A. **I think you would have to have reasonable data that would suggest that, you know, it's going to be worth the investment.**

Q. **And it's true, isn't it, that, at the time you left Allergan, you had evaluated a range of different concentrations for brimonidine. Right?**

A. **We evaluated a ton of different things. I think we had at least a couple of different concentrations of brimonidine.**

Q. **And we can agree that that included .2 percent 9115X.**

Correct?

A. **Yes, that was one of the formulations that we evaluated and you showed it to me.**

MR. BOGGS: I would like to look at the original claims of the '834 patent.

THE COURT: Mr. Boggs, about how much more cross do you have?

MR. BOGGS: I have about ten or 15 minutes.

THE COURT: I think we will recess for the evening. We will resume at 9:00.

(Court recessed at 6:00 p.m.)

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